



MEDICATION USE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

The incidence and prevalence of chronic kidney disease (CKD) has escalated in the past decade due to an ageing population, increased prevalence of diabetes and cardiovascular disease. This presents diverse challenges to the healthcare system. One such challenge relates to medication prescribing practices for patients with CKD. The process of selecting, prescribing and maintaining the correct drug dosing is challenging, partly because of CKD-induced changes in drug pharmacokinetics and pharmacodynamics. Further, there is high occurrence of chronic comorbidities and resultant multiple drug prescribing in patients with CKD. Providing optimal care to patients with CKD is an area of concern for health care professionals as there is evidence of suboptimal prescribing, particularly in older people. Age-related heterogeneity coupled with overall decline in bodily function puts older people at higher risk of drug toxicity. Identifying ways for optimising prescribing and minimising harm in this vulnerable population is increasingly a priority for health care providers and policy makers.

The overall aim of this thesis was to determine how to improve use of high-risk medications in patients with CKD in community settings. Five connected studies were conducted to address the overall aim and quantify the extent of prevalence of inappropriate prescribing of renally-cleared drugs and explore the factors associated with it. We also aimed to identify the system-level and practice-level confounding factors that serve as barriers to implementing evidence-based guidelines in CKD care and to determine the intervention strategies most likely to have an effect in overcoming the observed barriers. The findings of this thesis provide a basis for designing intervention programs to optimise prescribing in patients with CKD in community settings.

The first part of this thesis quantified the extent of the prevalence of inappropriate prescribing of renally-cleared drugs in elderly patients living in the Australian community and aged care settings, and determined the factors associated with inappropriate prescribing. A key observation from this study was that, despite the existence of published guidelines for dosage adjustments based on renal function, aged care residents and community-dwelling older people are often prescribed renally-cleared medicines that are either contraindicated or above the recommended dosage. Over one-quarter ($n=1135$ out of 4035; 28.1%) of the patients prescribed the renally-cleared drugs examined had evidence of inappropriate prescribing of at least one of the drugs, based on renal function. The drugs/drug class most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan,

bisphosphonates and strontium. The factors independently associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs were; advancing age (odds ratio (OR)=1.06 per year increase, 95% confidence interval [CI] 1.05-1.07, $P<0.001$), the total number of renally-cleared drugs prescribed (OR=1.44 per unit increase, 95% CI 1.29-1.61, $P<0.001$), presence of diabetes (OR=1.51, 95% CI 1.30-1.76, $P<0.001$), presence of heart failure (OR=1.38, 95% CI 1.13-1.69, $P<0.005$) and living in aged care facilities (OR=1.28, 95% CI 1.06-1.55, $P<0.05$).

The second part of this thesis explored the factors contributing to inappropriate prescribing in detail. The asymptomatic nature and opportunistic diagnosis of CKD are considered to be some of the major reasons for the higher prevalence of inappropriate prescribing. Other contributing factors reported include prescribers' lack of knowledge of medications requiring dosage adjustment, the presence of renal impairment being overlooked by prescribers, underestimation of potential adverse events, and the lack of evidence-based data to guide prescribers on precautions and dosage adjustments. Moreover, a lack of quantitative data in the available drug information sources, and contradiction and inconsistency in dosing information may augment the problem of dosing error. Based on this background, we evaluated five standard drug information sources (*Australian Medicines Handbook*, *British National Formulary*, *American Hospital Formulary System*, *Monthly Index of Medical Specialties*, *Drug Prescribing in Renal Failure*) for the availability and concordance of renal dosing recommendations for 61 drugs recommended to be used with caution in renal impairment. We observed a lack of consistency among the sources regarding the definition and categorisation of CKD. Only a slight agreement was observed in the renal dosing recommendations among the sources (Fleiss Kappa: 0.3). Qualitative data were not well defined, and there was a lack of consistency in quantitative values. Some drugs marked as contraindicated in one source were not mentioned as such in others. Also, drugs considered as not requiring dosage adjustment in one source had explicit recommendations in other sources. We concluded that a lack of data to guide the prescribers on dosage adjustments and lack of consistency among the standard information sources could potentially contribute to inappropriate prescribing.

In the third part of the thesis, we investigated the extent to which renal dosing information was available in the manufacturer's product information (PI) and determined the concordance in renal dosing recommendations across the 155 brands of 27 drugs. For each brand, the PI was consulted and data referring to renal impairment was collated. The renal dosing recommendations varied significantly among different brands of the same drugs. Also,

there was inconsistency in use of CKD terminology and classification of renal impairment. There was generally a lack of detailed information in the PI regarding the use of drugs in patients with renal impairment. The majority of PI documents (88 of 155 PI; 57%) provided quantitative recommendations regarding dosage adjustments for renal impairment, but this was often not detailed enough to help users make an informed decision. For 37 PI documents (24%), an altered dosage regimen was proposed without a quantifiable measure of renal function reported in the dose recommendation. The results of pharmacokinetic studies in patients with renal impairment were not presented in 59 PI documents (38%). Twenty brands did not have full PI and advice such as “contact the manufacturer” was given. Four PIs mentioned the lack of data regarding use in patients with renal impairment and thus recommended avoiding the drug in renally impaired patients. We concluded that a lack of data to guide the prescribers on precautions and dosage adjustments and lack of consistency among the PIs could potentially contribute to inappropriate prescribing.

In the fourth part of the thesis, we determined the agreement among the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) and the CKD-Epidemiology Collaboration (CKD-EPI) equations, if hypothetically used in dosing of renally-cleared drugs in primary care settings. There was a significant difference in the kidney function values estimated from the three equations. There was a good overall agreement among doses rendered using the equations. Dosing based on either CrCl or an eGFR with body surface area normalisation removed appeared acceptable and practicable for the purpose of dosing of non-critical drugs in the primary care settings. However, it is worth noting that in some instances there were potentially important discrepancies among the doses rendered from the equations so caution should be exercised.

In the fifth part of the thesis, we conducted a survey of general practitioners (GPs) to determine what sort of implementable strategies are most likely to have an effect on GPs to improve renal dosing in patients with CKD. There was a low familiarity with CKD management guidelines and a general lack of confidence in identifying and performing dosage adjustment of renally-cleared drugs among the GPs. There was a general scepticism concerning the usefulness, reliability and applicability of the information sources for renal dosing. The major barriers to using guidelines were lack of easy access during consultations and ambiguous recommendations on renal dosing between the different sources. The factors responsible for inappropriate prescribing from the GPs’ perspective were a lack of awareness on the availability of information sources and a lack of practice of routine monitoring of renal

function. The most favoured interventions were decision support systems, online education training and medication reviews by pharmacists.

In the last part of the thesis, we also conducted a systematic review to explore the nature and types of interventions conducted by pharmacists for patients with CKD and the outcomes. Pharmacist-mediated drug use evaluation and monitoring appeared promising in decreasing the rate of over dosing, usage of unnecessary drugs and improving physician adherence to dosing guidelines. The high level of acceptance of pharmacists' recommendations by the physicians indicates the greater opportunity for pharmacists to be involved in CKD care.

In conclusion, optimising prescribing in patients with CKD requires accurate identification of CKD in clinical settings and individualisation of medication prescribing based on the patient's renal function, pharmacokinetic parameters and goals of care. Updating the information sources to present the key elements in an unambiguous format, in conjunction with efforts to build consensus among the standard information sources, seems necessary. As a result, GPs can easily incorporate the recommendations into daily practice. Regular updating of the content of drug information sources is also warranted. An emphasis should be placed on conducting and disseminating large population-based studies focused on determining the correct drug dosage based on renal function. The provision of more complete pharmacokinetic data in special groups, such as those with renal impairment, should be compulsory for the registration of new drugs. An expiry date should be assigned for PIs in order to enforce upgrading of the information over time. Improved dissemination of existing guidelines, online education to increase awareness of dosage problems in patients with CKD and adopting decision support systems to aid GPs in identifying and dosing renally-cleared drugs, also appear warranted.

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ABBREVIATIONS

ACEIs	Angiotensin-Converting Enzyme Inhibitors
AHFS	American Hospital Formulary System
AIHW	Australian Institute of Health and Welfare
AMH	Australian Medicines Handbook
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
ARBs	Angiotensin Receptor Blockers
AusDiab	Australian Diabetes, Obesity and Lifestyle Survey
BEACH	Bettering the Evaluation and Care of Health
BMI	Body Mass Index
BNF	British National Formulary
BSA	Body Surface Area
CARI	Caring for Australians with renal impairment
CKD	Chronic Kidney Disease
CKD-EPI	CKD-Epidemiology Collaboration
CVD	Cardiovascular Disease
DRIRF	Drug Prescribing in Renal Failure
DVA	Department of Veteran Affairs
eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HDL	High Density Lipoprotein
HMR	Home Medicine Review

KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQI	Kidney Disease Quality Initiative
KHA	Kidney Health Australia
LDL	Low Density Lipoprotein
MDRD	Modification of Diet in Renal Disease
MIMS	Monthly Index of Medical Specialities
NHS	National Health Survey
NICE	National Institute for Health and Clinical Excellence
NKF	National Kidney Foundation
PDA	Personal Digital Assistance
PTH	Parathyroid hormone
RMMR	Residential Medication Management Review
SrCr	Serum Creatinine

Chapter 1 INTRODUCTION

1.1 Thesis background

Chronic kidney disease (CKD) is one of the most common causes of preventable death in Australia. It is an important therapeutic problem due to its increased prevalence and a close association with substantial mortality and morbidity.¹ CKD is characterised by the occurrence of kidney damage and the progressive and irreversible loss of a patient's kidney function over a period of 3 months or more.² The major health outcomes of CKD include complications associated with impaired kidney function, development of cardiovascular disease (CVD) and progression to kidney failure.³ It is a global public health problem affecting more than 50 million people worldwide, with more than 1 million of them receiving kidney replacement therapy.⁴ The incidence and prevalence of CKD has escalated in the past decade with the increased prevalence of risk factors such as diabetes and hypertension.⁵ However, early diagnosis, optimal use of medications, treatment of comorbid conditions, management of complications, patient education and preparation for kidney replacement therapies, have all been associated with better outcomes in patients with CKD.^{2 6} At each CKD stage, patients benefit from measures that delay or prevent the progressive loss of kidney function, such as appropriate selection of medication and the reduction of cardiovascular risk factors.³ Avoidance of nephrotoxic drugs and dose modification of renally-cleared medications play a crucial role in preventing and delaying the drug-related adverse outcomes in patients with CKD.⁷

There have been national and international attempts to improve the detection and management of CKD.⁸ Various national and international nephrology bodies have released CKD management guidelines in recent years. Specialised texts have been designed to guide the dosing of medications in patients with CKD. However, despite their wide promulgation, a growing body of evidence suggests CKD is underdiagnosed and under-treated.^{9 10} Studies have indicated that inappropriate prescribing of renally-cleared medicines is common in patients with renal impairment both in Australia and internationally.⁹⁻¹⁵

There is a need to identify and understand the factors that serve as enablers for inappropriate prescribing in order to improve the usage of high-risk medications in patients with CKD. It is essential to understand barriers to implementing evidence-based guidelines in CKD care. This will assist in developing strategies to enhance the uptake of the guidelines in the clinical setting. Understanding what sort of intervention strategies would potentially have

an effect on GPs would facilitate designing and implementing structured intervention programs aimed to improve the overall prescribing and quality of care in CKD.

This thesis reports on work that investigated the extent of inappropriate prescribing of renally-cleared drugs in elderly patients in the Australian community and determined the associated factors. This thesis also identifies the system-level and practice-level confounding factors that serve as barriers to implementing evidence-based guidelines in CKD care.

1.2 Aim of the thesis

The general aim of this thesis was to investigate the magnitude of the issue and determine how to improve use of high-risk medications in patients with CKD in the community setting.

The aims of the specific studies were as follows.

- i. Evaluate the extent of inappropriate prescribing of renally-cleared drugs in elderly patients in the Australian community and determine the associated factors.
- ii. Examine the standard drug information sources for the availability and concordance of renal dosing recommendations.
- iii. Investigate the nature and the extent to which renal dosing information was available in the manufacturer's product information (PI) and determine the concordance in renal dosing recommendations across the various brands of the same drug.
- iv. Determine the agreement among the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) and the CKD-Epidemiology Collaboration (CKD-EPI) equations, if hypothetically used in dosing of renally-cleared drugs in primary care settings.
- v. To understand the options available to GPs to assist in managing medications in patients with CKD and to assess GPs' views on applicability, utility and potential barriers to using the available guidelines and information sources for drug dosing purposes in primary care settings.

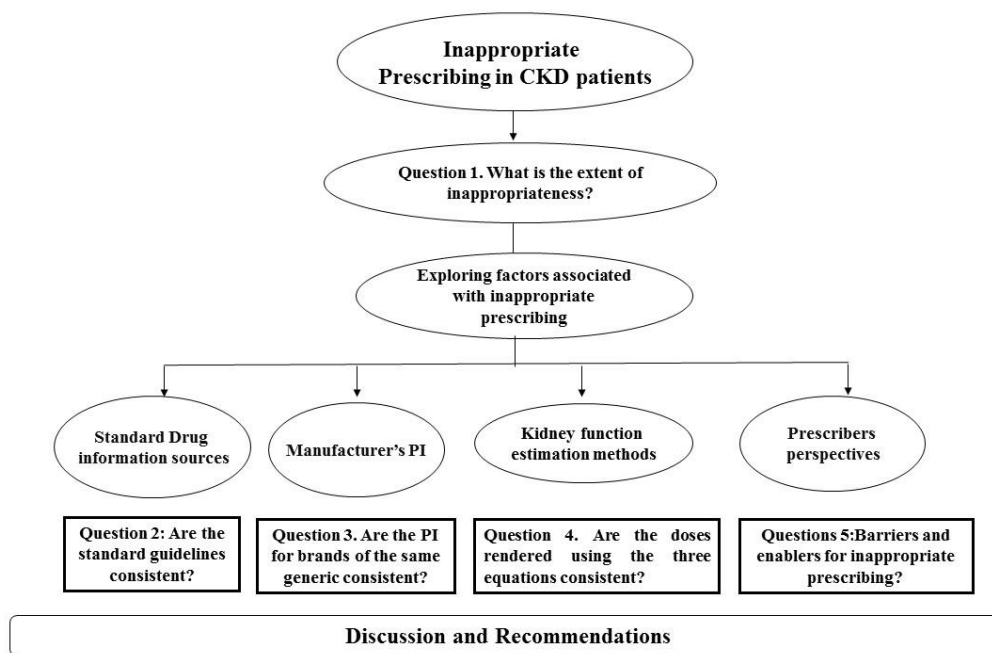


Figure 1.1 Thesis Structure

1.3 Rationale of the thesis

Studies have examined the dosing appropriateness of primarily renally-cleared medicines in hospital and nursing homes settings, and recommended the need for general education and raising awareness of medications requiring dosage adjustment, along with the need for routine assessment of renal function.⁹⁻¹⁵ However, the prevalence of inappropriate prescribing in patients with renal impairment in community settings has received relatively little attention, particularly in Australia; there is limited data on the prevalence of inappropriate prescribing of renally-cleared drugs in older community-based patients. The research outlined in this thesis investigated the extent of inappropriate prescribing of renally-cleared drugs in elderly patients in the Australian community setting.

A clear understanding of the factors that influence prescribing and guideline adoption is essential for improving the usage of medications, and ensuring optimal care and outcomes for patients with CKD. This thesis explored these factors in greater depth than previously reported. There is limited information available on the potential barriers to optimal management of medications in CKD from the prescriber's perspective. Little is known about the information sources that GPs use when deciding on drug doses for patients with CKD. To date, there have not been any studies conducted to identify GPs' perspectives regarding the

applicability and utility of these guidelines in patients with CKD in Australia. We were interested in undertaking a survey to understand the options available to GPs to assist in managing medications in patients with CKD and to assess GPs' views on applicability, utility and the potential barriers to using the available guidelines and information sources for drug dosing purposes in primary care settings.

Studies have reported a knowledge gap, limited educational and administrative resources for CKD management and a lack of awareness of estimated glomerular filtration rate (eGFR) and its correct usage as some of the reasons for suboptimal CKD management practices in the primary care settings.^{16-22 23 24} This thesis elaborates more upon the results of these studies by examining factors beyond those of GPs' knowledge and understanding, to identify system-level and practice-level confounding factors that serve as barriers to implementing available evidence-based guidelines for prescribing in patients with CKD.

This thesis determines the type of strategies that are most likely to have useful input in GPs' care of patients in order to improve prescribing in patients with CKD. The findings and benefits of this research will accrue indirectly and in the long term as this provides a framework for designing intervention programs in the primary care settings, aimed to reinforce knowledge about CKD and the available guidelines, drug use problems in CKD, and to improve the quality of care in CKD.

Chapter 2 LITERATURE REVIEW

2.1 Chapter Introduction

This chapter presents a background review on CKD covering the definition, classification, causes, and its risk factors. Additionally, CKD epidemiology, and its comorbidities and complications, will be reviewed. This is followed by an overview on the effect of renal impairment on drug pharmacokinetics and drug dosing considerations for patients with CKD with a focus on drugs that need to be used with caution. Emphasis will be placed on the methods used to assess renal function, a step by step approach to dose adjustment and the most commonly used CKD management guidelines and information sources developed to guide prescribers in renal dosing.

CKD is a general term that encompasses all degrees of decreased renal function, from patients at risk of damage to kidney failure through mild, moderate, and, severe impairment. CKD is recognised as a significant global health problem and should be managed in its early stages. CKD can be detected with routine laboratory tests and early intervention can prevent and delay its progression, reduce complications and therefore, improve both the likelihood of survival and quality of life for CKD patients. With a growing elderly population and increasing numbers of patients with diabetes and hypertension, the prevalence of CKD will continue to rise. As a result, primary health care practitioners will be confronted with the management of complex medical problems that are unique to CKD patients.

2.2 Chronic Kidney Disease

2.2.1 Definition and classification

Glomerular filtration rate (GFR) is accepted as the best overall measure of kidney function.² The normal level of GFR varies according to age, gender and body size. Normal GFR in young healthy adults is approximately 120 to 130 mL/min/1.73 m². A GFR level of less than 60 mL/min/1.73 m² indicates a loss of half or more of the adult level of normal kidney function.⁶ Below this level the risk of complication of CKD increases. In the past, the definition of CKD has been vague , with use of imprecise terminology such as ‘pre-dialysis’, ‘pre-end-stage renal disease’ ‘chronic renal insufficiency’, ‘chronic renal disease’, ‘chronic renal impairment’ and ‘chronic renal failure’ and has been categorised mainly by cause.²⁵ CKD should in principle, be classified in accordance with severity, diagnosis, treatment and prognosis, and consistently linked with “clinical action plans” to facilitate management.²⁶ In

2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) established a classification system for CKD that has been accepted and used worldwide.² “This classification defines CKD as a measured GFR or eGFR¹ of less than 60 mL/min/1.73 m² for three months or more, with or without kidney damage, or kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either: pathologic abnormalities, or markers of kidney damage, including haematuria or albuminuria or abnormalities in imaging tests.”² This evidence-based classification categorises CKD into five stages according to the level of kidney function with a clinical action plan, as shown below in Table 2.1. The Kidney Health Australia CARI (Caring for Australians with Renal Impairment) guidelines further categorise the stage 3 CKD into stage 3A (GFR=45-59 mL/min/1.73 m²) and stage 3B (GFR= 30-44 mL/min/1.73 m²).²⁶

Stage	Description	GFR (mL/min/1.73m ²)	Clinical action*
	At increased risk	≥90 (with CKD risk factors)	Screening, CKD risk reduction
1	Kidney damage with normal or ↑GFR	≥90	Diagnosis and treatment, Treatment of comorbidities, Slowing progression, CVD risk reduction
2	Kidney damage with mild ↓GFR	60-89	Estimating progression
3	Moderate ↓GFR	30-59	Evaluating and treating complications
4	Severe ↓GFR	15-29	Preparation for kidney replacement therapy
5	Kidney Failure	<15 (Dialysis)	Replacement (if uraemia is present)
GFR: Glomerular Filtration rate, CVD: cardiovascular Disease			

Table 2.1 Classification of CKD

*Includes action from preceding stage, shaded area identifies patients who have CKD, unshaded area delineates individuals who are at increased risk for developing CKD.

¹ eGFR stands for estimated Glomerular Filtration rate, derived using the GFR predicting equations that combine serum creatinine value with patient factors such as age, gender and weight.

2.2.2 Causes and risk factors

The causes for CKD, as defined above, are not well established. However, the causes for end stage renal disease (ESRD) as encountered in Australia are; diabetic nephropathy (32% of all new patients), glomerulonephritis (24%), hypertension (14%) and reflux nephropathy (3%). (Figure 2.1) The major risk conditions for patients with CKD are hypertension, diabetes, obesity and dyslipidaemia.²⁷

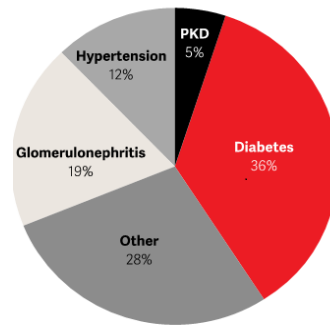


Figure 2.1 Causes of end stage renal disease

Source Collins *et al* (2009)²⁷

The various risk factors for CKD are as follows.²⁸

Socio-environmental factors: Socioeconomic status, nature of environment, availability of health care²⁸

Biomedical risk factors: Diabetes, high blood pressure, metabolic syndrome, obesity, urinary tract infections, kidney and urinary stones, glomerulonephritis, streptococcal infections, drug toxicity²⁸

Behavioural risk factors: Tobacco smoking, physical inactivity, poor diet²⁸

Predisposing factors: Age, gender, ethnicity, family history, genetic makeup²⁸

2.2.3 Clinical presentation

Patients usually present themselves to their physicians when a significant loss of kidney function occurs. Up to 90% of the renal function can be lost before the clinical symptoms of CKD become apparent; therefore, routine screening and monitoring is important.²⁹ Patients with CKD may not notice any symptoms until they reach ESKD requiring dialysis or a

transplant (GFR <15 mL/min/1.73m²). The symptoms of ESKD include lethargy, nocturia, malaise, anorexia, nausea, pruritus, restless legs and dyspnoea.³⁰

2.2.4 Comorbidities and complications

Diabetes, hypertension, cardiovascular disease, and anaemia are common in patients with CKD and managing them is a challenge.³¹ The prevalence of these comorbidities increases as CKD progresses (Figure 2.2).³² Most patients (86%) with advanced CKD have at least one comorbidity.³³ Early detection and intervention has shown to reduce the progression of CKD and its complications, and primary care providers have an important role in the diagnosis and management of comorbidities in patients with CKD.³⁴ It is essential to regularly check for the known complications of CKD and to monitor treatment targets.

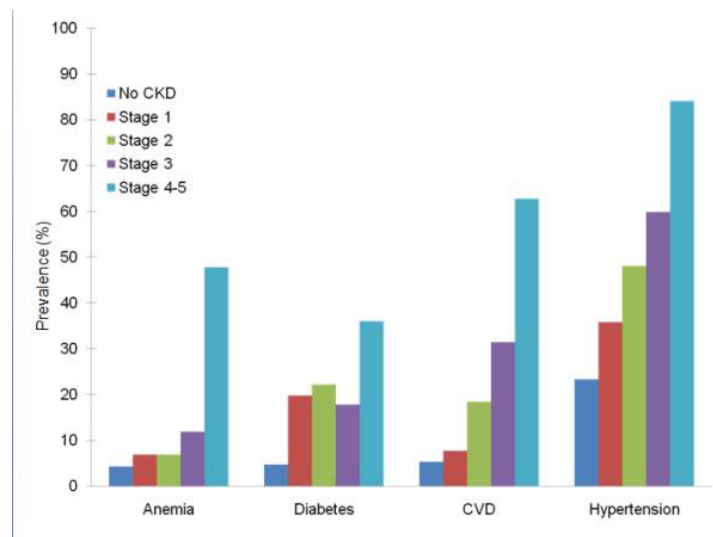


Figure 2.2 Prevalence of comorbidities by CKD stages³²

Hypertension

Hypertension is both a cause of CKD and a complication of CKD, and can be difficult to control. Hypertension is associated with accelerated progression of CKD, increased risk of developing and worsening of coronary heart disease and stroke.³⁵ The prevalence of hypertension is 84% in patients with stage 4–5 CKD, compared with 23% of adults without CKD.³² In addition, up to 75% of patients with CKD have blood pressure levels > 140/90 mm Hg, more than 10 mm Hg above the current treatment target in CKD. CKD with hypertension is a compelling indication for the use of angiotensin-converting enzyme inhibitors (ACEIs) or

angiotensin receptor blockers (ARBs) as first-line therapy.³⁶ With the initiation of treatment with ACEIs or ARBs, GFR may reduce and the potassium level may rise.³⁷ If the acute decrease in GFR is less than 25% below the baseline level and stabilises within two months, the medication should be continued. If the reduction in GFR is greater than 25% below baseline value, these drugs should be stopped and the patient should be examined for bilateral renal artery stenosis.³⁸ If the serum potassium concentration is greater than 6 mmol/L despite dose reduction, diuretic therapy and dietary potassium restriction, then the medication should be stopped. Combined therapy of ACE inhibitor and ARB is not recommended.³⁸

Hyperkalaemia

Almost one-fourth of patients with stage 5 CKD experience a life-threatening episode of hyperkalaemia that requires emergency treatment. The incidence of hyperkalaemia is low in patients with stage 3 CKD but may develop with ACEI or ARB therapy. In more severe CKD, use of ACEIs or ARBs and the presence of diabetes have been found to be associated with the increased frequency and severity of hyperkalaemia.³⁹ Measures to lower serum potassium should be initiated if the concentration exceeds 5 mmol/L. Reduction of ACEI, ARB, and beta-blocker dosages and the use of loop diuretics or a combination of loop and thiazide diuretics, and treatment with alkali replacement in patients with acidosis also can effectively manage hyperkalaemia.

Diabetes

Patients with diabetes are at an increased risk for CKD and cardiovascular events. The patients with diabetes require intensive blood glucose control in order to reduce the risk of developing microalbuminuria, macroalbuminuria and/or overt nephropathy.⁴⁰ Glycaemic control is challenging in patients with CKD because of increased sensitivity to medications and adherence issues related to the complexity of the regimen.⁴¹ Patients with stage 3–5 kidney disease have an increased risk of hypoglycaemia due to decreased medication clearance and impaired kidney gluconeogenesis.⁴² Therefore, glucose levels should be monitored closely and treatment should be adjusted slowly to reduce the risk of hypoglycaemia.

Drugs for diabetes should be used with correct dose adjustment. The Australian Medicine Handbook recommends avoiding glibenclamide in patients with CKD.⁴³

Glibenclamide and other long-acting sulfonylureas are more likely to induce serious hypoglycaemia in CKD patients.^{44 45} Some of the metabolites of glibenclamide that have hypoglycaemic activity are likely to accumulate in patients with CKD and this increases the risk of hypoglycaemia.⁴⁵⁻⁴⁷ Brier et al reported an increase in elimination half-life of glibenclamide from 3.3 hours to 5.0 hours in haemodialysis patients.⁴⁸ Several studies have reported decreased elimination of glibenclamide in patients with CKD resulting in increased risk of hypoglycaemia and have recommended using caution in patients with CKD.⁴⁹⁻⁵¹

Metformin is contraindicated in severe renal impairment and has been recommended to be used with caution in mild to moderate impairment due to the risk of lactic acidosis.⁴³ As metformin is entirely cleared by the kidneys, it may accumulate when renal function decreases, with the potential for exposure-dependent toxicity that could precipitate lactate accumulation.⁵² However, several observational studies have failed to show a consistent link between metformin and lactic acidosis.⁵⁴⁻⁵⁷ The incidence of lactic acidosis associated with metformin therapy in CKD patients is usually low and metformin is not necessarily responsible when lactic acidosis occurs in patients taking this medication.^{55 58} Studies show that although drug levels are higher in those with kidney dysfunction, levels are still maintained largely within the therapeutic range and lactate levels are not substantially increased when metformin is used in patients with renal impairment.^{53 59 60} A recent review also reported that the rate of lactic acidosis in patients taking metformin was similar to people with diabetes mellitus who did not take metformin.⁵⁵ There have been increasing calls to update the metformin-prescribing guidelines to allow for use of this drug in patients with mild to moderate CKD.^{61 62} However, to date there are no randomised controlled trials conducted in patients with mild to moderate CKD to determine if metformin is safe.

Mineral and bone disorder

The metabolism of calcium, phosphate, parathyroid hormone (PTH) and vitamin D are adversely affected due to renal impairment.⁶³ When GFR falls below 60 mL/min/1.73m², the renal clearance of phosphate is decreased. This results in a higher level of serum phosphate. With the decline of kidney function, there is decline in the level of calcitriol, the most active form of vitamin D, which is synthesised in the kidney. Subsequently, the calcium level falls as there is less calcitriol dependent calcium uptake from the gastrointestinal tract. The cumulative effect of elevated phosphate level, and diminished calcium and vitamin D level, stimulates

parathyroid hormone production.⁶⁴ The elevated levels of PTH increase the resorption and release of mineral from bone. This leads to an increased risk of fracture.⁶⁵

Anaemia

The prevalence of anaemia increases markedly with decreasing GFR. Anaemia related to CKD usually occurs at GFR less than 60 mL/min/1.73m² and is more prominent in patients with severe CKD.³² Anaemia of CKD is related to reduced erythropoietin production by the kidney. Treatment with erythropoietin agents improves health-related quality of life but it has been found to increase risk of stroke and other cardiovascular events. CKD patients with anaemia should be evaluated for iron deficiency and treated with oral or parenteral iron when indicated before using erythropoietin agents ⁶⁶

Cardiovascular disease

About 63% of patients with advanced CKD encounter cardiovascular events compared with 5.8% of adults without CKD.³² Patients with CKD are more likely to die from cardiovascular diseases than progress to dialysis, and cardiovascular events account for 45% of deaths in dialysis patients.³⁵ Conditions like hypertension, dyslipidaemia, diabetes, anaemia and other metabolic abnormalities increase the likelihood of occurrence of cardiovascular events in patients with CKD. Prevention and treatment of cardiovascular disease in CKD involves addressing these factors.

Dyslipidaemia

CKD is associated with substantial abnormalities of lipid metabolism, including increased low-density lipoproteins, triglycerides, very-low-density lipoproteins, and reduced levels of high-density lipoprotein cholesterol.⁶⁷ Dyslipidaemia is more severe in individuals with proteinuria, particularly those with nephrotic syndrome. Dyslipidaemia should be treated as per CVD recommendations and targets.⁶⁷

Other comorbidities

In addition to the comorbidities outlined above, patients with CKD are more likely than those without CKD to have acidosis, osteoporosis, depression, and sexual dysfunction.^{68 69} Identifying and treating these comorbidities may significantly improve quality of life for patients with CKD. Depression can affect 1 in 5 people with CKD and 1 in 3 individuals on dialysis.⁶⁸ It has detrimental effects on mortality, rates of hospitalisation, medication and treatment adherence, nutrition, and overall quality of life.

2.3 An overview of CKD in Australia

CKD is the 9th leading cause of death in Australia.⁷⁰ CKD is a stronger risk factor for coronary events and all-cause mortality than diabetes.²⁸ One in 10 Australian adults have indicators of CKD including reduced kidney function and/or albumin in the urine. Approximately 1.7 million Australians aged 18 years and over had some biomedical signs of CKD.^{70 71} Fewer than 10% of people with CKD are aware they have this condition. This equates to over 1.5 million Australians being unaware that they have indicators of CKD.²⁸ Risk factors for chronic kidney disease are highly prevalent in Australia and the number of Australians at risk is increasing. Indigenous Australians in particular are at high-risk. Aboriginal and Torres Strait Islanders have a greater prevalence of CKD and are approximately 10 times more likely than non-Indigenous Australians to develop end stage renal disease.⁷² It is most prevalent in remote areas and is strongly correlated with socioeconomic disadvantage.⁷²

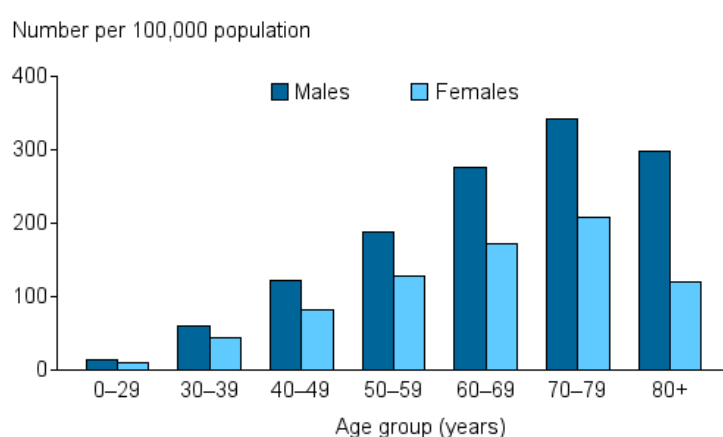


Figure 2.3 Prevalence of treated end stage kidney disease in Australia, by age and sex 2013

Source: AIHW analysis of Australia and New Zealand Dialysis and Transplant Registry data⁷⁰

There were over 1.6 million hospitalisations where CKD was the principal and/or additional diagnosis in 2013-14.⁷³ This represented 17% of all hospitalisations in Australia.⁷³ Dialysis accounted for the majority of (81%) of these hospitalisations (Figure 2.4).

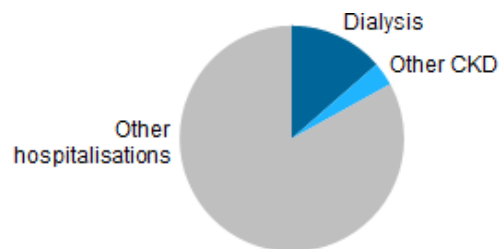


Figure 2.4 Reason for hospitalisations in Australia

Source: Australian Institute of Health and Welfare⁷³

CKD accounts for 1 in 10 deaths in Australia.⁷³ It was an underlying or associated cause of 15,900 deaths recorded in 2013.⁷³ The frequency of hospitalisation and CKD-associated death was 3 to 5 times higher among Aboriginal and Torres Strait Islander Australians compared with non-Indigenous people.⁷²

2.4 Effect of Kidney disease on drug pharmacokinetics

Pharmacokinetic parameters like hepatic clearance, absorption, and renal clearance (tubular secretion, reabsorption, glomerular filtration rate) are affected adversely due to renal dysfunction.^{74 75} This alters the total clearance of drugs eliminated primarily by the kidney and guided dosing should be considered when prescribing these drugs to patients with CKD.⁷⁶ Renal impairment can also enhance the accumulation of active metabolites, which can lead to exaggerated therapeutic effect or undesirable pharmacologic activity or toxicity.⁷⁵

2.4.1 Effect on absorption

Renal dysfunction induces various physiological changes in the gastrointestinal tract, such as increased gastric pH, gastroparesis, bowel wall oedema, vomiting, diarrhoea, and reduced intestinal metabolism and transport. The aetiology of these changes are usually multifactorial.⁷⁷ For medications (such as furosemide, ketoconazole and ferrous sulphate) that are most soluble in an acidic environment, increased gastric pH often reduces drug dissolution

and ionization resulting in reduced bioavailability.^{75 77 78} Gastroparesis is a common manifestation in CKD, which can result in delayed gastric emptying and may prolong the time to maximum drug concentration.⁷⁷⁻⁷⁹ These delays are important for drugs such as short-acting sulfonylureas.⁷⁵ Bowel wall oedema has also been reported as a potential cause of diminished oral absorption in patients with CKD.^{74 75 77 79} Vomiting and diarrhoea are also common in patients with CKD, and can reduce the amount of drug absorbed.^{74 75} CKD is associated with decreased activity of intestinal cytochrome P450 enzyme activity.⁸⁰ This can have a profound effect by increasing overall oral absorption.^{77 79}

2.4.2 Effect on distribution

CKD-induced alteration in protein binding adversely affects the distribution of drugs and has significant clinical implications. CKD manifested uraemia results in lower concentration of albumin, a plasma protein to which the acidic drugs bind to. This hypoalbuminemia can result in an increased level of free concentration of acidic drugs such as barbiturates, furosemide, salicylates, warfarin, valproate, cephalosporin, penicillin and phenytoin. The plasma concentration alkaline drugs such as propranolol, morphine, oxazepam, vancomycin, that bind to α 1-acid glycoprotein are elevated in renal dysfunction. Thus, the free fraction of alkaline drugs is often elevated in renal dysfunction.^{74 75} CKD-induced alterations in body composition, such as increased total body water and decreased muscle mass, have a significant effect on hydrophilic drugs. There is an increase in volume of distribution of these drugs due to oedema and ascites. This leads to a reduction in serum concentration. However, the muscle wasting and increased adipose tissue may reduce volume of distribution and may result in increased serum concentration of hydrophilic medication.⁷⁵

2.4.3 Effect on metabolism

The kidney accounts for 15% of metabolic functions by the liver. Various metabolic enzymes are located in the cortex of the kidney. Both Phase I and Phase II reactions are profoundly affected by CKD.⁸⁰ The hydrolysis and reduction reactions are slowed in patients with CKD. Methylation (dobutamine, 6-mercaptopurine, dopamine), glucuronidation (morphine, acetaminophen/paracetamol, oxazepam, lorazepam, naproxen), sulfation (salbutamol, minoxidil, dopamine), acetylation (dapsone, hydralazine, isoniazid, procainamide) are slowed in patients with CKD. Reduction in overall metabolic rate leads to

increased concentration of parent drug in plasma, causing potential toxicity and various adverse drug outcomes.^{77 79}

2.4.4 Effect on excretion

The kidney is a major site for elimination of drugs. The renal elimination of drugs depends upon the GFR, which in turn is affected by the protein binding of drugs.⁷⁶ Drugs bound to protein are not filtered through the glomerulus. The filtration of drugs depends upon the concentration of the free drugs in plasma. In patients with CKD, there is a higher level of free drug in plasma but the GFR is decreased. Resultantly, the elimination half-life of the drug is prolonged. This leads to accumulation of the drug or of toxic metabolite or biological active metabolite of the drugs in the body.⁷⁶ A metabolite of pethidine, norpethidine (or normeperidine) has lower analgesic activity but its accumulation has adverse effects on the CNS, leading to convulsions.⁸¹

2.5 Methods to determine renal function

Accurate estimation of kidney function is an important component in the multifactorial care of patients with CKD.⁸² Knowledge of kidney function is essential for CKD staging and influences all aspects of pharmacological and non-pharmacological therapy.⁸² GFR, defined as the rate (volume per unit of time) at which filtrate is formed by the glomerulus, is considered the best indicator of overall kidney function and therefore its assessment has become an important clinical tool in the daily care of patients.

GFR cannot be measured directly, but instead it can be assessed by the renal clearance of a filtration marker that achieves stable plasma concentration, is inert, and is freely filtered by the glomeruli but not reabsorbed, secreted, or metabolized. Such an ideal endogenous marker does not exist. Serum creatinine, one of the clinically useful analytes endogenously produced by the muscle and excreted by the kidney (others are serum urea and, more recently, serum cystatin C), has long been used by clinicians as a marker of kidney function.⁸³ It is most useful for assessing minor changes in kidney function over time in the same individual.⁸⁴ However, serum creatinine should not be used alone as a measure of kidney function as it is influenced by a range of factors, such as age, gender, ethnicity, muscle mass, diet, drugs, and disease state.⁸⁵

The isolated use of serum creatinine concentration may not reflect the actual degree of kidney function in an individual as the the inverse relation between serum creatinine and GFR is nonlinear, particularly when patients have near-normal renal function. The serum creatinine concentration may be in the normal range while the patient's GFR may be markedly reduced, indicating impaired kidney function. This is common in older people who have decreased muscle mass along with overall decline in GFR.⁸⁵ Serum creatinine does not increase beyond normal limits until more than 50% of GFR has been lost (Figure 2.5).

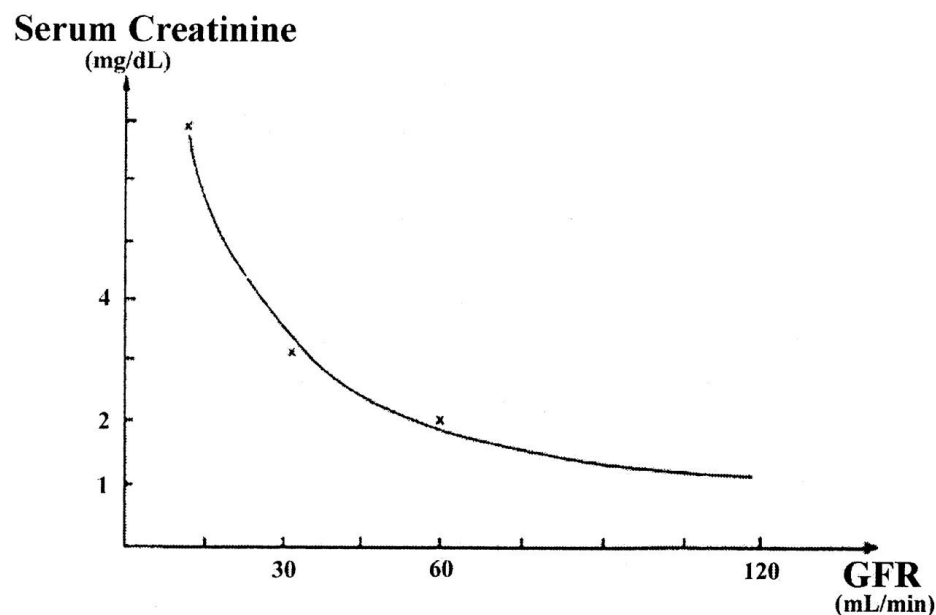


Figure 2.5 Curvilinear relationship between GFR and serum creatinine⁸⁶

Note that, on the right side of the graph, relatively large reductions in GFR result in only minor changes in serum creatinine, while the opposite relationship is demonstrated at the top of the graph.

An alternative to this approach is the measurement of creatinine clearance.

2.5.1 Measurement of Creatinine Clearance (CrCl)

GFR can be measured directly from the urinary clearance of an endogenous filtration marker such as creatinine derived from a 24 hr urine collection.⁸⁷ This is called 24-hour creatinine clearance (CrCl) measurement. This determination does not require highly trained personnel or expensive assays and can be performed by standard laboratories.

However, this method is limited by the difficulties in obtaining accurate urine collection and the associated delay in the reporting of the results.⁸⁸ It is often susceptible to error because of analytical interference of concomitant disease state and concurrent medications in the assay. This method, however, is widely available and familiar to the health care community.

2.5.2 Measurement of GFR using exogenous markers

GFR can be measured using exogenous substances, such as inulin and iohexol.⁸⁷ The inulin clearance measurement has been the gold standard of GFR evaluation. Inulin is an ideal filtration marker as it is simply filtered in the glomeruli and neither reabsorbed nor secreted.⁸⁹ Due to the limited availability of the substance and the labour intensity of the assay, this is rarely performed except for research purposes.⁹⁰ A few modifications to this procedure were introduced, such as use of radiolabelled markers such as iothalamate, iohexol, diethylenetriamine pentaacetate (DTPA), and ethylenediamine tetraacetate (EDTA).⁹¹ The plasma clearance of these radiolabelled markers was measured and there was no need for urine collections. Some of the limitations associated with this procedure are that some of the markers are not completely eliminated by GFR, but are also secreted by the tubules. The extrapolation of the area under the curve is required to calculate the plasma clearance of the exogenous markers. This is often unreliable in patients at moderate to severe stages of CKD or with oedema. In clinical practice, these methods are not feasible as the procedures are cumbersome, expensive and subject to error unless done under carefully controlled conditions.

2.5.3 Estimating GFR using serum creatinine based equations

GFR measurement using clearance of exogenous filtration marker is complicated in clinical practice as it requires substantial time and resources. Alternatively, GFR can be estimated in clinical practice from serum creatinine using prediction equations (eGFR). This method involves obtaining a blood sample to measure creatinine concentration and then combining it with patient factors using the GFR estimating equations to determine eGFR.⁹² The advantage of this method is that the results are available for routine clinical practice and it is highly practical in routine individual drug dose calculations. For the majority of people, GFR estimating equations are, on average, more accurate than measured creatinine clearance and provide an unbiased assessment of measured GFR. The National Kidney Foundation Disease Outcomes Quality Initiative recommends using eGFR estimated from prediction equations

based on serum creatinine, mainly due to the inadequacies of serum creatinine and a 24-hr CrCl.² The various equations to estimate GFR in clinical care settings are as follows:

2.5.3.1 Cockcroft-Gault equation

The Cockcroft-Gault equation predicts CrCl based on age, body weight, height, gender and plasma creatinine, together with correction factors.⁹³ This equation was derived from a study population of 249 Caucasian men aged 18 to 92 years, with and without CKD.⁹³ It is most widely used for estimating renal function and is the standard equation for calculating renal drug doses. The United States Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) recommend using CrCl estimated by the Cockcroft-Gault equation for guiding the renal dosing of drugs and for conducting pharmacokinetic studies.^{94 95}

$$eCrCl = [((140 - \text{age}) \times \text{weight}) / (72 \times \text{Scr})] \times 0.85 \text{ if female}$$

Note: eCrCl is expressed in mL/min, age is expressed in years, weight is expressed in kilograms, and Scr is expressed in mg/dL.

Limitations to using this equation include the use of unstandardized creatinine assays and differing reference materials. The CG equation cannot be re-expressed for isotope-dilution mass spectrometry (IDMS) traceable creatinine values. The creatinine method used in the development of the equation is no longer in use and samples from the study are not available. The CG equation underestimates GFR in the elderly and is less accurate in patients with normal kidney function. The CG equation provides CrCl that is not adjusted for body surface area (BSA). The requirement for weight and height to be provided restricts its ability to be reported by the laboratory. Modifications of the CG equation, such as the use of ideal versus actual body weight, were developed in an attempt to overcome the imprecision with the use of measured body weight.⁹⁶ However, there is no evidence that these modifications are more accurate predictors of GFR or provide better drug-dosing guidelines.

2.5.3.2 Modification of Diet in Renal Disease (MDRD)

The Modification of Diet in Renal Disease (MDRD) Study equation was derived from a study population of 1,628 men and women with CKD, aged 18 to 70 years, predominantly Caucasian, nondiabetic, and who were non-kidney-transplant recipients.⁹⁷ MDRD is normalised for race, BSA, age, and sex; it is reported as mL/minute/1.73 m². The MDRD Study

equation estimates GFR adjusted for BSA. Kidney function is proportional to kidney size, which is proportional to BSA. BSA of 1.73 m² is the normal mean value for young adults. MDRD is primarily used for CKD staging in clinical practice. Given the MDRD equation was developed from a population of patients with CKD, it is imprecise and underestimates GFR at higher values, yielding false positives for CKD.⁹⁸ Additionally, the MDRD equation has not been validated in individuals less than 18 years of age; individuals greater than 75 years of age; pregnant women; patients at extremes in body size; or in races other than Caucasian and African American.⁹⁹

The original MDRD Study equation is suitable for use with creatinine methods that do not have calibration traceable to IDMS. Calibration bias and measurement imprecision for plasma creatinine have a large impact on the eGFR.¹⁰⁰ To overcome the error from instrument bias, standardisation of creatinine measurements to the reference IDMS method, was introduced. With this, a new factor of ‘175’ (as opposed to ‘186’) was used in the MDRD equation for creatinine assays that are IDMS-aligned.¹⁰¹

Original MDRD equation⁹⁷

$$\text{eGFR} = 186 \times (\text{Standardised Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Note: GFR is expressed in mL/min per 1.73 m², Scr is serum creatinine expressed in mg/dL, and age is expressed in years.

Re-expressed MDRD Study equation¹⁰¹

$$\text{eGFR} = 175 \times (\text{Standardized Scr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Note: GFR is expressed in mL/min per 1.73 m², Scr is serum creatinine expressed in mg/dL, and age is expressed in years.

2.5.3.3 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the newest equation, normalises for race, BSA, age, and sex and is reported as mL/min/1.73 m².¹⁰² In clinical practice, CKD-EPI is most commonly used for CKD staging. The CKD-EPI is a more accurate estimation of GFR than MDRD at all values. The CKD-EPI formula is a useful tool to estimate

GFR in all people, including various ethnic populations.¹⁰² The CKD-EPI formula has been validated as a tool to estimate GFR in some non-Caucasian populations, including South-East Asian, African, Indian and Chinese individuals living in Western countries. A recent validation study confirmed that CKD-EPI formula (without the African American race correction factor), provides a reasonably unbiased and accurate estimate of GFR in Indigenous Australians.¹⁰³

CKD-EPI equation¹⁰²

For females with $\text{SCr} \leq 62 \mu\text{mol/L}$: $= 144 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.7)^{-0.329} \times (0.993)^{\text{age in years}}$

For females with $\text{SCr} > 62 \mu\text{mol/L}$: $= 144 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.7)^{-1.209} \times (0.993)^{\text{age in years}}$

For males with $\text{SCr} \leq 80 \mu\text{mol/L}$: $= 141 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.9)^{-0.411} \times (0.993)^{\text{age in years}}$

For males with $\text{SCr} > 80 \mu\text{mol/L}$: $= 141 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.9)^{-1.209} \times (0.993)^{\text{age in years}}$

The K/DOQI clinical practice guideline recommends using eCrCl calculated from the Cockcroft Gault equation or eGFR calculated from the MDRD or CKD-EPI study equation for routine estimation of kidney function.² However, both eGFR and eCrCl estimates may not be accurate in individuals at extremes of body size or muscle mass, particularly in populations with reduced muscle mass, including the frail, elderly and critically ill patients.¹⁰⁴ In these individuals for whom serum creatinine based estimates may be inaccurate, direct measurement of CrCl using 24-hr method or measurement of GFR using exogenous filtration markers should be considered.¹⁰⁵ Similarly, when dosing medications with narrow therapeutic indices or with high toxicity it is recommended to use measured GFR. The Australasian Creatinine Consensus group suggests that the eGFR calculated with the MDRD or CKD-EPI formula is acceptable to assist with drug dosing decisions in general practice.¹⁰⁶ Therefore, in addition to the CrCl calculated using Cockcroft-Gault equation, eGFR estimated using MDRD and CKD-EPI equations will also be used for determining doses for renally cleared drugs in this thesis. In chapter six, the agreement among all three equations in dosing of renally cleared drugs will be examined.

Above discussed methods for estimating kidney function are essential to detect renal impairment and to determine the need for dose adjustment of renally cleared drugs. Dose adjustment can be achieved by a reduction in dose, or an extension of the dosing interval, or both. Knowledge of appropriate dosage adjustment method is important to ensure drug effectiveness and to avoid accumulation and drug toxicity in patients with CKD.

2.6 Drug dosing considerations for patients with CKD

It is essential to understand the patient's renal function while prescribing medicines that are renally excreted.⁷⁶ The dose and the dosing interval of these medicines needs to be modified in patients with renal impairment, but the need for dosage adjustment is not always recognised. The impaired renal function can cause medicines or their metabolites to accumulate and potentially cause toxicity.⁸² This is common in medicines with a narrow therapeutic index (e.g, digoxin, lithium).⁷⁶ Renal function must be monitored in patients taking drugs that impair renal function or cause nephrotoxicity.^{76 107} Patients with pre-existing renal impairment are more prone to nephrotoxicity. Monitoring renal function is important regardless of the length of time a medicine has been used, as the dose needs to be changed as the patient ages (and renal function declines). Renal function must be assessed when: prescribing a new renally excreted or nephrotoxic medicine, even for drugs for chronic conditions.¹⁰⁸ (Table 2.2)

<u>Analgesics</u>	<u>Genitourinary</u>	<u>Blood</u>	<u>Endocrine</u>	
codeine	solifenacinb	dabigatran	glibenclamide	
hydromorphone	sildenafil	enoxaparin	glimepiride	
morphine	tadalafil	rivaroxaban	gliptins	
oxycodone	tolterodine		metformin	
tramadol	vardefafil			
<u>Neurological</u>	<u>Psychotropic</u>	<u>Cardiovascular</u>	<u>Gastrointestinal</u>	<u>Musculoskeletal</u>
baclofen	acamprosate	ACE-Is	H2-antagonists	allopurinol
gabapentin	amisulpride	ARBs		bisphosphonates
galantamine	benzodiazepines	atenolol		colchicine
levetiracetam	bupropion	bisoprolol		strontium
memantine	desvenlafaxine	digoxin		ranelate
methysergide	duloxetine	fenofibrate		teriparatide
paliperidone	lithium			
pramipexole	reboxetine			
pregabalin	venlafaxine			
topiramate				
varenicline				

Table 2.2 Drugs requiring dosage adjustment in renal impairment

This list contains drugs used commonly in Australian community setting. Therefore, it does not include antibiotic, antifungal or antiviral medicines, or those medicines predominately used in hospital settings

Source. Veterans Mates Therapeutic brief¹⁰⁸

Medicines that may accumulate and require renal function monitoring

Drugs and their metabolites may accumulate and contribute to exaggerated pharmacologic effects or adverse drug reactions in patients with CKD, especially if the medicine has a narrow therapeutic index (e.g. digoxin, lithium). Potential adverse effects can be prevented by reducing the dose, extending the dose interval, or by prescribing an alternative medicine that is less likely to accumulate.¹⁰⁹ It is necessary to consider that fixed dose combination products may also contain one or more active ingredients that are renally excreted. Some of medicines commonly prescribed in general practice that require dose modification on the basis of renal function monitoring are presented below.

Metformin

Metformin may accumulate in patients with renal impairment. This increases the risk of lactic acidosis, a rare but potentially fatal adverse drug reaction. This risk is highest in patients with comorbidities manifested by hypoxemic conditions, such as acute myocardial infarction, severe infection, respiratory disease, and liver disease.⁷⁶ Australian guidelines recommend a total maximum daily dose of 2000 mg for patients with a GFR of 60–90 mL/min, and 1000 mg for patients with a GFR of 30–60 mL/min.¹¹⁰ Metformin is not recommended for patients with a GFR <30 mL/min.

Dabigatran

Renal impairment may cause accumulation of dabigatran and lead to major bleeding and death.¹¹¹ It is recommended to assess renal function in all patients before starting dabigatran. Dabigatran is contraindicated in patients with GFR <30 mL/min.¹¹² For patients taking dabigatran, renal function should be assessed in situations where a decline in renal function is suspected (eg. hypovolaemia, dehydration, concurrent use of nephrotoxic medicines); in older patients or those with moderate renal impairment taking dabigatran, renal function should be assessed at least once per year.^{108 112}

Bisphosphonates

Bisphosphonates are not recommended for treating osteoporosis in patients with a GFR <30–35 mL/min.⁴³ There is a high risk of renal failure associated with zoledronic acid, especially in patients co-prescribed diuretics or other potentially nephrotoxic medicines.¹¹³ Drugs like strontium ranelate and teriparatide used to treat osteoporosis are also not recommended in patients with a GFR <30 mL/min.

Sulphonylureas

Renal impairment increases susceptibility of a patient to hypoglycaemia associated with sulphonylureas and their metabolites. Short-acting sulphonylureas (eg. glicazide, glipizide) are preferred choices for patients with renal impairment, as these drugs do not have an active metabolite and dose reduction is not usually necessary.^{43 109}

Opioids

A variety of opioids (codeine, tramadol, morphine, hydromorphone) have active metabolites, which can accumulate in renal impairment, causing central nervous system or respiratory depression; therefore, a dose reduction is necessary.¹¹⁴ It is recommended that the initial dose of oxycodone should be reduced in patients with a GFR <30 mL/min. Immediate release products need to be dosed less frequently.⁴³ Extended release products (eg. controlled release oxycodone) are potentially more difficult to titrate to appropriate clinical effect in those with renal impairment.

Allopurinol

The active metabolite of allopurinol, which is primarily renally cleared, accumulates in renal impairment causing adverse effects.¹⁰⁹ Therefore, dose adjustment is warranted. An initial dose of 100 mg on alternate days is recommended for patients with a GFR <10 mL/min, or if possible, the medicine should be avoided in this situation.⁴³ A maintenance dose of 100 mg/day is sufficient for the majority of older patients.

Medicines that can reduce renal function or cause nephrotoxicity

There are a number of commonly used medicines that can impair renal function or cause nephrotoxicity such as Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). In patients with renal impairment, drugs with toxic metabolites should be avoided, the least nephrotoxic agents should be used, and alternative medications should be prescribed if necessary to avoid potential drug interaction. In severe renal impairment, the remaining functional nephron units work harder to compensate for the loss of other nephrons. These residual nephrons are more susceptible to nephrotoxic injury due to their increased workload. If the use of nephrotoxic drug cannot be avoided, then therapeutic drug monitoring and renal function monitoring is mandatory.

ACEIs and ARBs

Renal impairment affects the excretion of most ACEIs and increases the risk of hyperkalaemia; therefore, dose adjustment may be necessary. Renal function and electrolytes level should be measured when initiating treatment with ACEIs or ARBs and these tests should be repeated after 1-2 weeks.¹¹⁵ ACEIs or ARBs can cause an acute decline in GFR, even without pre-existing risk factors. This decline is more significant, especially in presence of congestive heart failure, diuretic or NSAID use.³⁰ If the acute decline in GFR is greater than 25% below baseline, then the medicine should be stopped and investigations for bilateral renal artery stenosis should be performed.⁴³

NSAIDs

NSAIDs use is linked to three times higher risk for acute renal failure.¹¹⁶ Short-term NSAIDs use is well tolerated in absence of heart failure, diabetes, or hypertension and if the patient has normal renal function. Long-term use is not recommended as it can cause nephrotic syndrome with interstitial nephritis and chronic renal failure. The decline in GFR associated with NSAIDs may improve following treatment cessation.¹¹⁷ When NSAIDs are used together with either loop diuretics or ACEIs/ARBs, the risk of renal failure is further increased.¹¹⁸ For patients with renal impairment, paracetamol is considered suitable to use. Serum creatinine should be checked every 2 to 4 weeks in early treatment with NSAIDs.

Medicines causing biochemical changes

Drugs such as amiloride, eplerenone, and spironolactone are contraindicated in patients with severe renal impairment and it is advised to monitor renal function and potassium levels if used in renal impairment, due to the increased risk of hyperkalemia.⁴³ Products with a high sodium content (eg, some antacids) may cause sodium and water retention in patients with CKD. Excessive vitamin D replacement therapy, use of calcitriol have been found to precipitate or exacerbate renal impairment and increase the risk of hypercalcaemia and nephrocalcinosis in patients with CKD.

Spironolactone

Renal function monitoring for patients using spironolactone should be considered due to the risk of hyperkalemia.⁷⁶ This is particularly the case when spironolactone is used in combination with ACEs and ARBs, NSAIDs or in patients with diabetes.¹⁰⁹ In patients with a GFR less than 30mL/min, spironolactone is best avoided.

2.7 CKD management guidelines and resources

Various professional nephrology bodies around the world have designed and disseminated CKD management guidelines to provide guidance and clinical tips to help identify, manage and refer CKD in general practice (Table 3.2) The recommendations are formed from existing evidence-based clinical guidelines, current research, and clinical consensus. It is recommended that GPs and other health professionals consult these guidelines in order to ensure a high standard of care for their patients. Some of the most commonly accessed resources for information on drug use in CKD are shown below in Table 2.3.

<p>KDIGO Guideline: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2012 clinical practice guideline for the evaluation and management of CKD</p> <p>http://www.kdigo.org/clinical_practice_guidelines/CKD.php</p>
<p>CARI Guideline: Diagnosis, classification and staging of chronic kidney disease. July 2012.</p> <p>http://www.cari.org.au/CKD_early_CKD/Diag_Classification_Staging_ECKD.pdf</p>
<p>The Renal Association Guideline: for detection, monitoring and care of patients with CKD.</p> <p>http://www.renal.org/Clinical/GuidelinesSection/Detection-Monitoring-and-Care-of-Patients-with-CKD.aspx</p>
<p>Japanese Society of Nephrology Guideline: Evidence-based Practice Guideline for the Treatment of CKD. http://www.jsn.or.jp/en/guideline/pdf/guideline.2009.pdf</p>
<p>National Institute for Health and Clinical Excellence (NICE) Guideline: Early identification and management in adults in primary and secondary care. 2008, Royal College of Physicians.</p> <p>http://www.nice.org.uk/nicemedia/live/12069/42116/42116.pdf</p>
<p>Canadian Society of Nephrology Guideline: for management of chronic. CMAJ. 2008;179(11):1154-62.</p> <p>http://www.cmaj.ca/content/suppl/2008/11/17/179.11.1154.DC1</p>
<p>NKF KDOQI Guideline: CKD: evaluation, classification, and stratification. Am J Kid Dis.2002;39(2 Suppl 1): S11-266.</p> <p>http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm</p>

Table 2.3 CKD management guidelines

Drug Prescribing in Renal Failure: Dosing Guidelines for Adults.

<http://acp.pdaorder.com/pdaorder/-/6059205375541/item?oec-catalog-item-id=1028>

FDA Centre for Food Safety and Applied Nutrition

<http://www.cfsan.fda.gov/>

FDA MedWatch

<http://www.fda.gov/medwatch/index.html>

Medicine Plus

Web site: <http://www.nlm.nih.gov/medlineplus.html>

National Kidney Disease Education Program

Web site: <http://www.nkdep.nih.gov>

National Kidney Foundation

Web site: <http://www.kidney.org/>

Kidney Check Australia Taskforce (KCAT) program. Kidney Health Australia

Website: www.KCAT.org.au

PDA=personal digital assistant, FDA= U.S Food and Drug Administration

Table 2.4 Resources for information on drug use in CKD

2.8 Approach to renal drug dosing

Safe drug prescribing in patients with CKD can be complex and requires a stepwise approach. In order to ensure effectiveness, minimise further damage and prevent drug nephrotoxicity, the following recommendations may be useful.⁷⁵ (Figure 2.6).

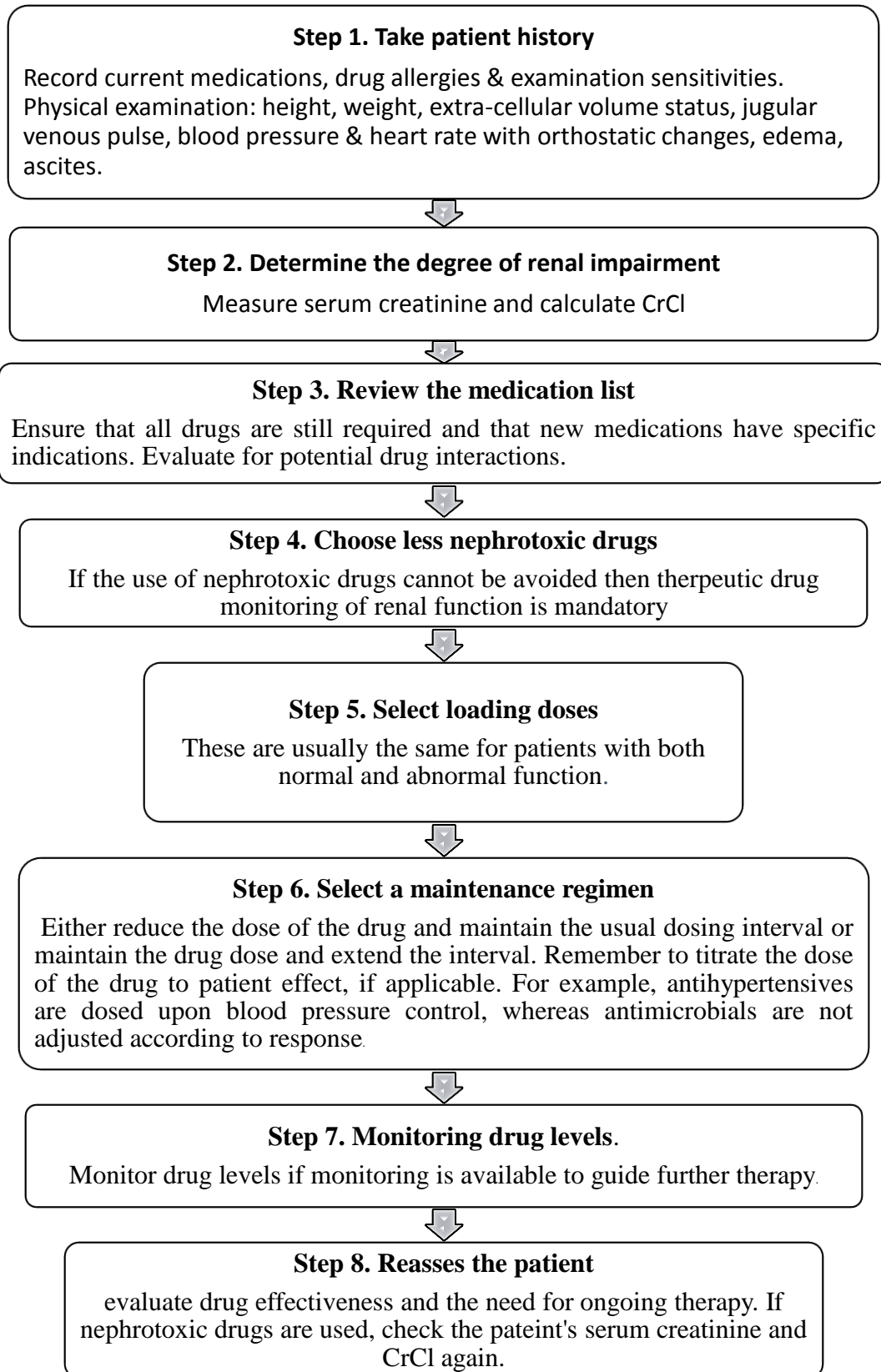


Figure 2.6 Step by step approach to dosage adjustment in renal impairment⁵⁸

Initial patient assessment

The first step is to have a detailed initial patient assessment that includes medical history, previous drugs, past medications, comorbidities, concurrent medications including over the counter drugs, body weight and height, laboratory data for renal function parameters, liver function tests and albumin concentration.^{74 75}

Evaluating the degree of renal impairment

The second step is to evaluate the degree of renal impairment. GFR is the most reliable index and surrogate marker of overall kidney function; however, in clinical settings it is not possible to measure GFR, therefore calculation of eGFR using the MDRD equation to determine the CKD stage is required.² Calculation of CrCl using Cockcroft-Gault equation to determine the appropriate drug dose adjustment is also necessary. Most medications may not require dose adjustment at CrCl>50 mL/min.

Reviewing the Medication List

Medications should be reviewed for any potential drug interactions and adverse effects.⁷⁵ It should be ensured that the appropriate drugs have been prescribed for the given indication.¹¹⁹ For patients with CKD or elderly patients with declining renal function, the doses of medicines for new and chronic conditions should be reviewed to ensure they are still suitable to the degree of renal function.⁷⁷ Dose adjustment is necessary to avoid toxicity in patients who are elderly or have rapidly declining renal function.

Choosing the drug that has no or Minimal Nephrotoxicity

In chronic kidney failure, the nephrons are more susceptible to nephrotoxic injury due to nephrotoxic drugs. It is recommended to avoid the use of nephrotoxic drugs; however, if used, then therapeutic drug monitoring and renal function monitoring is recommended.^{75 120 121}

Selecting the dose regimen

Loading doses usually do not need to be adjusted in patients with CKD, except for drugs that have a large volume of distribution.¹²² The recommendation for adjusting dose regimen can be obtained from drug information sources. Some of the most commonly used information sources are the Australian Medicine Handbook,⁴³ British National Formulary,¹²³ Drug Prescribing in Renal Failure⁸¹ MIMS¹²⁴ and the American Hospital Formulary System Drug Information.¹²⁵ The suggested methods for dose adjustments in these information sources are dose reduction, lengthening the dosing interval, or both. The dose reduction method involves reducing each dose while maintaining the normal dosing interval.⁷⁶ This approach maintains a constant drug concentration, but is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of sub-therapeutic drug concentrations, especially toward the end of the dosing interval.⁷⁶

Information sources provide dose recommendations for individual drugs corresponding to different levels of CKD. The guidelines are divided into broad GFR categories usually encompassing up to a 10-fold range in renal function. Quantitative data on dose adjustment based on various categories of renal impairment is well suited for renal dosing purposes; however, not all drugs have quantitative data on dose adjustment in renal impairment. Therefore, regimens must be individualized further based on patient response and serum drug concentrations. Clinical judgement should be used and doses must be adapted to the specific patient's situation. There are factors other than renal impairment that influence the choice of drug and its dose. The severity of the condition being treated, the toxicity of the drug, comorbidity, and the patient's size, age, and gender, all have an influence on the dosing of CKD patients. It might be necessary to titrate the dose according to the patient's clinical condition or quantitative measures for example- international normalised ratio, heart rate, blood pressure.

Monitoring Outcomes

It is recommended to monitor drug levels if monitoring is available to guide therapy. For drugs with a narrow therapeutic index, such as aminoglycosides, digoxin and lithium, it is mandatory to monitor the drug level. For certain drugs like antihypertensive and oral hypoglycaemic, the

dose may be titrated based on pharmacodynamic response (e.g. monitoring of blood pressure, blood sugar and glycated haemoglobin).⁷⁴

2.9 Inappropriate prescribing

Inappropriate prescribing has been defined as the use of a particular medicine that poses greater risk of harm than benefit, especially when safer and more effective options are available for the same condition.¹²⁶ Inappropriate prescribing has become an area of major concern in patients with CKD, especially in older people.⁷⁷ One of the most important prescribing problems in patients with CKD is medication dosing errors.¹²² It is generally acknowledged that certain drugs should be used cautiously or avoided completely in this patient group, if a safer alternative is available.⁷⁵ Because of the pharmacokinetic and pharmacodynamics changes associated with CKD, the patients are more susceptible to adverse effects.¹⁰⁷ In the case of patients with CKD, the most common form of inappropriate prescribing is the use of an inappropriately high dose based on the renal function or contraindicated drug.¹⁰ The concept of inappropriate prescribing recognises that there are no medications without any risk, whereby appropriate use of medications requires that the benefits associated with its use outweigh the risks.¹²⁷

Various studies have been conducted to address the dose appropriateness and dose adjustment practice in hospital settings in Australia and overseas; however, there is very limited data in the community setting.¹²⁸⁻¹³³

A cross-sectional study conducted in the Princess Alexandra Hospital, Queensland, Australia in patients with renal impairment found that 111 (44.8%) of 248 prescriptions of the targeted drugs were inappropriately high.¹²⁸

In a prospective study in a hospital setting in France, Solomon *et al* found that out of the 886 prescriptions for patients with CKD, 34% prescriptions were inappropriate.¹³¹ Among these, 14% were contraindicated and 20% were inappropriately high doses based on renal function.

A longitudinal study analysing the inpatients record of four years in South Korea revealed that 5.3% of the prescribed drug doses were excessive based on the patient's renal function.¹³⁴ The rate of overdosing in patients with moderate to severe CKD was 28.2%. Out of the 56 drugs studied, 10 drugs including piperacillin, amoxicillin and ranitidine accounted

for 85.4% of the overdoses. Chertow *et al* analysed 17,828 prescriptions in a tertiary care hospital in the USA and reported that 70% of the prescriptions for nephrotoxic or renally-cleared medications in renally impaired patient were inappropriate.¹³⁵ Decloedt *et al* reported that out of 615 prescriptions for 97 patients with CKD, drug adjustment was required in 19% of cases and only 32% of the prescriptions had the correct dose adjustment in a hospital setting in Africa.¹³⁶

A high proportion of elderly patients, ranging from 12-43%, are reported to have been administered excessive doses of primarily renally-cleared medicines in various studies conducted in nursing homes and hospital settings around the world.^{9 10 12} Approximately 20–50% of elderly people in the Australian community setting are prescribed one or more potentially inappropriate medicines, with higher rates seen in residential aged care facilities.^{132 137-139} These studies examined the inappropriate use of medicines in elderly patients and was not confined to those where dose adjustment was required due to decline in renal function. In our thesis we will be examining the inappropriate use of medicines focusing on the elderly population who require dose adjustment due to decline in renal function.

About 43% of the elderly patients received at least one of 20 renally-cleared drugs inappropriately in a cohort of 456 patients in four long-term care facilities in Canada.⁹ The drugs most frequently prescribed inappropriately were allopurinol, glibenclamide, ranitidine and metformin, and variables like age, weight, number of medications and the number of physicians prescribing in the facility were predictive for receiving an inappropriate prescription based on CrCl.⁹

Approximately 12% of the patients had evidence of inappropriate prescribing of at least one of 21 renally-cleared drugs in a longitudinal study of 3804 elderly patients in 133 nursing homes in the USA and factors associated with potentially inappropriate prescribing were age older than 85 years, obesity and multiple comorbidities.¹⁰ In a cross sectional study conducted by Rahimi *et al* in the USA, 50% of the patients were prescribed with renally-cleared drugs and 25% of them had at least one medication dosed incorrectly for renal function.¹² A recent study in aged care residents in Australia has recognised metformin and perindopril as the top most inappropriately prescribed drugs in aged care settings.¹⁴⁰ The inappropriate prescribing of oral hypoglycaemics, angiotensin receptor blockers (ARBs), angiotensin-converting-enzyme-inhibitors (ACEIs) and drugs for the treatment of bone diseases for elderly patients with renal impairment has been noted in various studies.^{9 11 133}

2.10 Next Step

This chapter suggests that despite the availability of CKD management guidelines and information sources to help guide renal dosing, patients with renal impairment continue to be exposed to inappropriate prescribing around the world. In Australia, a high proportion of elderly patients are reported to have been administered inappropriate prescribing in various studies conducted in nursing homes and hospital settings, and this proportion was higher in nursing home patients. In the next section, we quantify the extent of inappropriate prescribing for renally-cleared drugs in elderly patients in Australian community settings and residential aged care facilities, and determine the factors associated with inappropriate prescribing.

Chapter 3 POTENTIALLY INAPPROPRIATE PRESCRIBING OF RENALLY-CLEARED DRUGS IN ELDERLY PATIENTS IN COMMUNITY AND AGED CARE SETTINGS

The literature outlined in Chapter 2 discussed the various CKD management guidelines and the recommended approach to drug dosing in patients with CKD. Evidence suggests that older people are more vulnerable to inappropriate prescribing as they often have multiple comorbidities, aged related heterogeneity, and an overall decline in renal function, for which clinicians, using evidence-based guidelines, should prescribe the recommended therapy with dose adjustment. The aim of this chapter was therefore to determine the prevalence of inappropriate prescribing for renally-cleared drugs in elderly patients and determine the factors associated with inappropriate prescribing.

3.1 Abstract

Background

Limited data is available on the prevalence of inappropriate prescribing for renally-cleared drugs in elderly patients in Australia.

Objectives

To quantify and compare the extent of inappropriate prescribing (defined as at least one drug prescribed in excessive dose or when contraindicated with respect to renal function) for renally-cleared drugs in elderly patients across the community and aged care settings, and to determine factors associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs.

Methods

This retrospective study examined de-identified Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) cases pertaining to 30,898 patients aged 65 years and over. Only 25% (n=7625) of these patients had documented information on renal function. Among them, 4035 patients were prescribed at least one of the 31 renally-cleared drugs examined in the study. For these patients, details including demographics, medications, medical conditions and pathology test results were extracted. The creatinine clearance (CrCl) was estimated using the Cockcroft-Gault formula and the prevalence of inappropriate prescribing for the 31 drugs was examined, based on conformity with the recommendations in the Australian Medicines Handbook. Multivariate logistic regression was

performed to determine the factors associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs.

Results

The mean age (SD) of the HMR (n=3315; 59% female) and RMMR (n=720; 68% female) patients were 78.3 ± 7.2 and 86 ± 7.3 years, respectively. Over one-quarter (n=1135 out of 4035; 28.1%) of the patients prescribed the renally-cleared drugs examined had evidence of inappropriate prescribing of at least one of the drugs, based on renal function. The drugs/drug class most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium. The factors independently associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs were; advancing age (odds ratio (OR)=1.06 per year increase, 95% confidence interval [CI] 1.05-1.07, $P < 0.001$), the total number of renally-cleared drugs prescribed (OR=1.44 per unit increase, 95% CI 1.29-1.61, $P < 0.001$), presence of diabetes (OR=1.51, 95% CI 1.30-1.76, $P < 0.001$), presence of heart failure (OR=1.38, 95% CI 1.13-1.69, $P < 0.005$) and living in aged care facilities (OR=1.28, 95% CI 1.06-1.55, $P < 0.05$).

Conclusions

Inappropriate prescribing of renally-cleared drugs is common in older Australians. Intervention studies to improve prescribing of renally-cleared drugs in the elderly appear warranted.

Key Points

- Aged care residents and community dwelling older people are often prescribed renally-cleared medicines that require dose adjustment based on renal function, outside of the recommended guidelines. 25.9% of the HMR patients and 37.9% of RMMR patients received inappropriate prescribing for at least one of the renally-cleared drugs examined in the study.
- The drugs/drug class most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium.
- The factors independently associated with patients being prescribed one or more renally-cleared drugs inappropriately were advancing age, the total number of renally-cleared drugs prescribed, presence of diabetes, presence of heart failure and living in aged care facilities.
- It is essential to consider renal function when prescribing renally-cleared drugs to elderly patients. The need for dosage adjustment should be determined by measurement of the renal function and the optimal dose should be determined by consulting standard drug information sources.
- Designing an intervention program targeted towards improving the prescribing of these medications seems necessary.

3.2 Introduction

Providing optimal care to the aging population has been, and is increasingly, an area of concern for health care professionals.¹⁴¹ The process of selecting, prescribing and maintaining the correct drug dosing is challenging in the elderly, partly because of the high prevalence of chronic disease states and resultant multiple drug prescribing.^{142 143} Furthermore, age-related heterogeneity coupled with overall decline in bodily function put these patients at high-risk of toxicity.^{144 145} The glomerular filtration rate (GFR) decreases gradually at an average rate of 0.8 mL/min/1.73 m²/year after age 40 years and this decline accelerates after about age 65 to 70 years.¹⁴⁶⁻¹⁴⁸ Therefore, optimal drug selection and dosing modification should be carried out in elderly patients in order to avoid the occurrence of adverse drug events (ADEs), particularly for renally-cleared drugs.^{85 149}

The need for drug dosage adjustment can be determined by measurement of the renal function of patients.¹⁵⁰ Previous overseas studies conducted in hospital settings and nursing homes have revealed that a high proportion of elderly patients are administered excessive doses of primarily renally-cleared medicines.⁹⁻¹⁵ Subsequently, the problem of dose inappropriateness has been addressed to some extent, by general education and raising awareness of medications requiring dosage adjustment and the need for routine assessment of renal function.¹² Approximately 20–50% of elderly people in the Australian community setting are prescribed one or more potentially inappropriate medicines, with higher rates seen in residential aged care facilities.^{132 137-139} Pharmacist conducted medication reviews have found to be effective in reducing the use of potentially inappropriate medicine for elderly people in the Australian community.¹³⁹ However, the prevalence of inappropriate prescribing in patients with renal impairment in community settings has received relatively little attention; particularly in Australia, where there is limited data on the prevalence of inappropriate prescribing of renally-cleared drugs in older community-based patients.

Given this background, we conducted this study to quantify and compare the extent of inappropriate use of renally-cleared drugs in older patients across the community and aged care settings, and to determine the factors associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs.

3.3 Methods

3.3.1 Ethics and data source

Ethical approval for the study protocol was granted by the Tasmanian Health and Medical Human Research Ethics Committee Tasmania, Australia (H0012386). This retrospective study examined a sample of de-identified Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) cases pertaining to older Australians. HMR and RMMR are community-based collaborative services provided by general practitioners (GPs) and accredited pharmacists.¹⁵¹ HMR services are provided to the community-dwelling older individuals whereas RMMR services are available to all permanent residents of Australian Government-funded aged care facilities. When requested by a GP, an accredited pharmacist conducts an HMR/RMMR. Information about the patient's medicines is collated and a comprehensive assessment is undertaken to identify, resolve and prevent medication-related problems. A report of this assessment is provided to the GP. Based on this report, the GP and the patient develop and implement a medication management plan.

3.3.2 Data extraction

The RMMR and HMR services were conducted by accredited pharmacists in collaboration with GPs between January 2010 and June 2012. These de-identified cases were extracted from the database of Medscope, an IT company providing decision support solutions for accredited pharmacists performing medication reviews. Approximately 12% of Australian accredited pharmacists performing medication reviews utilise this system. This database includes information on each patient's medical conditions, medication and biochemical parameters. Demographic data (age, sex, weight), medical conditions, pathology test results and medications (including doses) were extracted into a database developed in Access 2010 (Microsoft Corporation, Redmond, USA).

3.3.3 Inclusion criteria

All individuals aged 65 years and older, who had their serum creatinine reported and were prescribed one or more of the drugs under review, were included in the study. We used a list of 31 renally-cleared drugs that are prescribed commonly in the community setting and recommended to be avoided or used with dose adjustment in older patients by the Department of Veterans' Affairs (DVA), Australia (Appendix 1).¹⁵²

A total of 30,898 elderly patients (aged 65 years or over) were identified in the database. Those who had their renal function reported (n=7625) were selected for further analysis. Out of these, a total of 4035 patients who were taking at least one of 31 renally-cleared drugs in our list, were included in the final sample. The creatinine clearance (CrCl) was estimated using the Cockcroft-Gault (CG) equation.⁹³ For 1604 patients (1417 HMR, 187 RMMR) whose CrCl could not be estimated due to lack of reported weight, the laboratory eGFR provided in the database was used. For each drug, prescriptions were marked as “appropriate dosage” when the prescribed dose was in conformity with the adjustment specified in Australian Medicines Handbook (AMH)¹⁵³ with regard to the patient’s renal function. Prescriptions were considered as “inappropriate dosage” when the dose exceeded that recommended for the patient’s renal function. Prescriptions were considered as “contraindicated” if AMH recommended avoiding use in renal impairment based on the patient’s renal function. Both “inappropriate dosage” and “contraindicated” were treated as inappropriate prescription. Inappropriate prescribing is defined as a situation where risk from the adverse effects of a prescribed medication outweighs the desired clinical benefits of treating a particular condition.¹²⁷ It includes over-use of medications at a higher frequency or for longer durations than clinically indicated and the use of multiple medicines that have recognised drug-drug interactions.¹⁵⁴ For our study purpose, we defined potentially inappropriate prescribing as use of a contraindicated medication or inappropriately high dose according to the renal function. Similar definitions for inappropriate prescribing in renal impairment have been reported in past studies.^{9 10 155} For example, metformin prescribed at a dose of 2000 mg one daily to a patient with a calculated CrCl of greater than 60 mL/min would be considered appropriate, whereas the same prescription in an individual of CrCl less than 60 mL/min would be inappropriate.

3.3.4 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. and Excel 2010 (Microsoft Corporation, Redmond, USA). Descriptive statistics were presented as median, mean, standard deviation and range, depending on normality. Univariate analysis (Mann-Whitney and Chi square test) followed by multivariate logistic regression, were performed to determine factors associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs.

The dependent variable was presence or absence of inappropriate prescribing for at least one of the 31 drugs examined, based on the patient's renal function. The independent variables included age, sex, setting (home or aged care facility), total number of drugs prescribed, total number of chronic medical conditions, and the number of renally-cleared drugs prescribed from our list. Also included were dichotomous variables (presence or absence) for heart failure, diabetes and hypertension, which have previously been recognised as major contributing factors for renal impairment.^{10 34} The independent variables with probability values (P) ≤ 0.1 in the univariate analysis were entered in to the multivariate logistic regression analysis using the Enter method. All variables were assessed for multicollinearity prior to inclusion in the logistic regression model. The probability for stepwise entry was set at 0.01 and removal at 0.1 including constant in the model. A P-value of < 0.05 was considered as statistically significant.

3.4 Results

3.4.1 Patients' characteristics

The study sample included 4035 elderly patients, who had their renal function reported and were prescribed with at least one of the 31 renally-cleared drugs under review. Approximately 18% ($n=720$) of these patients were residents from aged care facilities (i.e. RMMR cases) and 82% ($n=3315$) were from the community setting (i.e. HMR cases). The mean (SD) age of the HMR patients was 78.3 (7.2) years and for RMMR patients was 86 (7.3) years. There was a female predominance in both settings: aged care (67.6%) and community (59.4%). A high level of polypharmacy was identified in the study sample. The mean (SD) number of drugs prescribed per patient was 12.9 (4.6) and 13.5 (4.8) in aged care and community settings, respectively (Table 3.1).

Characteristics	HMR		RMMR	
	Number (%)	Mean \pm SD	Number (%)	Mean \pm SD
Setting	3315 (82.2)		720 (17.8)	
Demographics				
Age		78.3 \pm 7.2		86.0 \pm 7.3
Sex				
Male	1346 (40.6)		233 (32.4)	
Female	1969 (59.4)		487 (67.6)	
Health status				
Number of diagnoses per patient		10.03 \pm 5.8		8.5 \pm 3.7
Number of medications per patient		13.5 \pm 4.8		12.9 \pm 4.6
Number of renally-cleared drugs from the drug list		1.4 \pm 0.7		1.2 \pm 0.5
eCrCl				
Mean (SD) mL/min		62 \pm 23		50 \pm 24
Median (range) mL/min		60 (4-165)		46 (6-168)
CKD stages ^a				
Stage 1	422 (12.7)		56 (7.8)	
Stage 2	1279 (38.6)		131 (18.2)	
Stage 3	1422 (42.9)		396 (55)	
Stage 4	176 (5.3)		125 (17.3)	
Stage 5	16 (0.5)		12 (1.7)	
Medical conditions				
Hypertension	2691 (81.2)		431 (59.8)	
Diabetes	1677 (50.5)		307 (42.6)	
Heart failure	381 (11.4)		146 (20.2)	
HMR- Home medicines review, RMMR- Residential medication management review, eCrCl- estimated creatinine clearance, CKD- Chronic kidney disease				

Table 3.1 Patient Characteristics

3.4.2 Prescribing pattern for renally-cleared drugs

The majority of patients, 69.4% (n=2801 out of 4035), were prescribed only one renally-cleared drug from our list; 24.4% (n=986 out of 4035) patients were prescribed two drugs from the list. Only 6.1% (n=248 out of 4035) patients were prescribed three or more renally-cleared drugs from the list. Perindopril (n=762) and metformin (n=762) were the most commonly prescribed renally-cleared drugs among the patients who were on a single drug. Concomitant prescribing of perindopril with metformin (n=341), perindopril with bisphosphonates (n=185) and metformin with bisphosphonates (n=143) were most common in patients who were prescribed with two or more drugs.

3.4.3 Extent of inappropriate prescribing

Over one-quarter (n=1135 out of 4035; 28.1%) of patients in the study sample had evidence of inappropriate prescribing of at least one of the renally-cleared drugs and this included prescribing in excessive dose (80.6%; n=915 out of 1135), or when contraindicated (19.4%; 220 out of 1135). Overall, 71.8% patients (n=2900 out of 4035) in the study sample received appropriate doses based on their renal function.

The incidence of inappropriate prescribing was higher in the RMMR patients; 25.9% of the HMR patients and 37.9% of RMMR patients received inappropriate prescribing for at least one of the renally-cleared drugs ($P<0.001$). The drugs/drug class most commonly prescribed inappropriately were perindopril, fenofibrate, glibenclamide, gliptins, metformin, olmesartan, bisphosphonates and strontium (Table 3.2). The extent of inappropriate prescribing for each drug, comparison of HMR and RMMR for inappropriate prescribing of individual drug and the top most inappropriately prescribed drugs across HMR and RMMR are shown in the Table 3.3, Table 3.4 and Table 4.5 respectively.

Category	Drugs	Number of patients n (%)			
		Total	Not required	Higher dose (n)	Contraindicated
Top five drugs prescribed most inappropriately with high dose	Perindopril	1387	600 (43.2)	612 (44.1)	-
	Fenofibrate	205	85 (41.4)	85 (41.5)	1 (0.4)
	Saxagliptin	15	11 (73.3)	4 (26.7)	-
	Sitagliptin	183	127 (69.3)	41 (22.5)	-
	Vildagliptin	51	36 (70.5)	11 (21.5)	-
Top five drugs prescribed most inappropriately when contraindicated	Glibenclamide	29	20 (68.9)	-	9 (31.0)
	Alendronate	543	454 (83.6)	-	89 (16.3)
	Strontium	160	139 (86.8)	-	21 (13.2)
	Risedronate	457	412 (90.2)	-	45 (9.8)
	Olmesartan	71	66 (92.9)	-	5 (7.0)
Total inappropriate High dose + contraindicated	Perindopril	1387	600 (43.2)	612 (44.1)	-
	Fenofibrate	205	85 (41.4)	85 (41.5)	1 (0.4)
	Glibenclamide	29	20 (68.9)	-	9 (31)
	Saxagliptin	15	11 (73.3)	4 (26.7)	-
	Sitagliptin	183	127 (69.3)	41 (22.5)	-
	Vildagliptin	51	36 (70.5)	11 (21.5)	-
	Metformin	1514	203 (13.4)	272 (17.8)	54 (3.5)

Table 3.2 Top most inappropriately prescribed drugs

Drugs	Number of Patients				
	Total	NR	HD	CI	A
Alendronate	543	454 (83.6)	-	89 (16.3)	-
Clodronate	2	-	-	-	2 (100)
Risedronate	457	412 (90.2)	-	45 (9.8)	-
Zoledronic acid	130	124 (95.3)	-	6 (4.6)	-
Ibandronic acid	1	-	-	-	1 (100)
Strontium	160	139 (86.8)	-	21 (13.2)	-
Teriparatide	4	4 (100)	-	-	-
Perindopril	1387	600 (43.2)	612 (44.1)	-	175 (12.6)
Olmesartan	71	66 (92.9)	-	5 (7.0)	-
Valsartan	78	75 (96.1)	2 (2.6)	-	1 (1.2)
Fenofibrate	205	85 (41.4)	85 (41.5)	1 (0.4)	34 (16.5)
Metformin	1514	203 (13.4)	272 (17.8)	54 (3.5)	985 (65.0)
Glibenclamide	29	20 (68.9)	-	9 (31)	-
Sitagliptin	183	127 (69.3)	41 (22.5)	-	15 (8.2)
Saxagliptin	15	11 (73.3)	4 (26.7)	-	-
Vildagliptin	51	36 (70.5)	11 (21.5)	-	4 (7.8)

Drugs	Number of Patients				
	Total	NR	HD	CI	A
Rivaroxaban	1	1 (100)	-	-	-
Dabigatran	102	77 (75.4)		1 (0.9)	24 (23.5)
Duloxetine	113	103 (91.1)	6 (5.3)	-	4 (3.5)
Pregabalin	139	56 (40.2)	5 (3.5)	-	78 (56.1)
Gabapentin	128	28 (21.8)	14 (10.9)	-	86 (67.1)
Levetiracetam	30	10 (33.3)	6 (20)	-	14 (46.6)
Memantine	13	11 (84.6)	2 (15.3)	-	-
Paliperidone	3	1 (33.3)	-	-	2 (66.7)
Pramipexole	99	68 (68.6)	-	-	31 (31.3)
Varenicline	14	14 (100)	-	-	-
Solifenacin	84	81 (96.4)	-	-	3 (3.6)
Tolterodine	6	6 (100)	-	-	-
NR: Dose adjustment not required based on renal function, HD: Inappropriately high dose, CI: Contraindicated, A:Appropriate dose, “-“:Not applicable					

Table 3.3 Extent of inappropriate prescribing for each drug

Drugs	Number of HMR Patients					Number of RMMR Patients				
	Total	NR	HD	CI	A	Total	NR	HD	CI	A
Alendronate	431	372 (86.3)	-	59 (13.7)	-	112	82 (73.2)	-	30 (26.7)	-
Clodronate	1	-	-	-	1 (100)	-	-	-	-	1 (100)
Risedronate	382	351 (91.9)	-	31 (8.1)	-	75	61 (81.3)	-	14 (18.6)	-
Zoledronate	119	113 (94.9)	-	6 (5)	-	11	11 (100)	-	-	-
Ibandronate	1	-	-	-	1 (100)	-	-	-	-	-
Strontium	127	116 (91.3)	-	11 (8.7)	-	33	23 (69.6)	-	10 (30.3)	-
Teriparatide	2	2 (100)	-	-	-	2	2 (100)	-	-	-
Perindopril	1089	538 (49.4)	450 (41.3)	-	101 (9.2)	298	62 (20.8)	162 (54.3)	-	74 (24.8)
Olmесartan	69	66 (95.6)	-	3 (4.3)	-	2	-	-	2 (100)	-
Valsartan	76	73 (96)	2 (2.6)	-	1 (1.3)	2	2 (100)	-	-	-
Fenofibrate	189	82 (43.3)	75 (39.7)	1 (0.52)	31 (16.4)	16	3 (18.7)	10 (62.5)	-	3 (18.7)
Metformin	1326	184 (13.8)	241 (18.1)	32 (2.4)	895(67.5)	188	19 (10.1)	31 (16.4)	22 (11.7)	117 (62.2)
Glibenclamide	27	19 (70.3)	-	8 (29.6)	-	2	1 (50)	-	1 (50)	-
Sitagliptin	168	126 (75)	32 (19)	-	10 (6)	15	1 (6.6)	9 (60)	-	5 (33.3)
Saxagliptin	13	10 (76.9)	3 (23.1)	-	-	2	1 (50)	1 (50)	-	-
Vildagliptin	48	34 (70.8)	10 (20.8)	-	4 (8.3)	3	2 (66.6)	1 (33.3)	-	-
Rivaroxaban	1	1 (100)	-	-	-	-	-	-	-	-
Dabigatran	93	70 (75.3)	-	1 (1.07)	22 (23.6)	9	7 (77.7)	-	-	2 (22.2)
Duloxetine	87	82 (94.2)	4 (4.6)	-	1 (1.1)	26	21 (80.7)	2 (7.6)	-	3 (11.5)
Pregabalin	125	50 (40)	5 (4)	-	70 (56)	14	6 (42.8)	-	-	8 (57.1)
Gabapentin	96	24 (25)	10 (10.4)	-	62 (64.6)	32	4 (12.5)	4 (12.5)	-	24 (75)
Levetiracetam	22	6 (27.2)	5 (22.7)	-	11 (50)	8	4 (50)	1	-	3 (37.5)
Memantine	6	5 (83.3)	1 (16.6)	-	-	-	7 (100)	-	-	-
Paliperidone	1	-	-	-	1 (100)	-	1 (50)	-	-	1 (50)
Pramipexole	73	54 (74)	-	-	19 (26)	6	14 (53.8)	-	-	12(46.1)
Varenicline	13	13 (100)	-	-	-	-	1 (100)	-	-	-
Solifenacin	77	74 (96.1)	-	-	3 (3.9)	-	7 (100)	-	-	-
Tolterodine	6	6 (100)	-	-	-	-	-	-	-	-

Table 3.4 Extent of inappropriate prescribing: a comparison of HMR and RMMR

NR: Dose adjustment not required, HD: Inappropriately high dose, CI: Contraindicated, A: Appropriate dose, “-”: Not applicable

Category	HMR %	RMMR %
Top five drugs prescribed most <u>inappropriately with high dose</u>	Perindopril (41.3) Fenofibrate (39.7) Saxagliptin (23.1) Vildagliptin (20.8) Sitagliptin (19)	Fenofibrate (62.5) Sitagliptin (60) Perindopril (54.3) Saxagliptin (50) Vildagliptin (33.3)
Top five drugs prescribed most inappropriately in a <u>contraindicated condition</u>	Glibenclamide (29.6) Alendronate (13.7) Strontium (8.7) Risedronate (8.1) Zoledronic acid (5)	Glibenclamide (50) Strontium (30.3) Alendronate (26.7) Risedronate (18.6) Metformin (11.7)
Total inappropriateness High dose+ contraindicated	Perindopril (41.3) Fenofibrate (40.2) Glibenclamide (29.6) Saxagliptin (23.1) Vildagliptin (20.8) Metformin (20.5) Sitagliptin (19)	Fenofibrate (62.5) Sitagliptin (60) Perindopril (54.3) Saxagliptin (50) Glibenclamide (50) Vildagliptin (33.3) Strontium (30.3) Metformin (28.1)
HMR- Home medicines review, RMMR- Residential medication management review		

Table 3.5 Top most inappropriately prescribed drugs: a comparison of HMR and RMMR

Of the variables tested against inappropriate prescribing in the univariate analysis, age, residential aged care setting, number of renally-cleared drugs prescribed, presence of hypertension, diabetes and heart failure were associated (at $P \leq 0.1$) whilst the number of diagnoses, number of medications, and sex were not. Table 3.6 presents the results of multivariate logistic regression analysis. The factors independently associated with patients being prescribed one or more renally-cleared drugs inappropriately were advancing age (odds ratio (OR)=1.06 per year increase, 95% confidence interval [CI] 1.05-1.07, $P < 0.001$), the total number of renally-cleared drugs prescribed (OR=1.44 per unit increase, 95% CI 1.29-1.61, $P < 0.001$), presence of diabetes (OR=1.51, 95% CI 1.30-1.76 $P < 0.001$), presence of heart failure (OR=1.38, 95% CI 1.13-1.69, $P < 0.005$) and living in aged care facilities (OR=1.28, 95% CI 1.06-1.55, $P < 0.05$).

Variables	p-value	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Age in years	<0.001 ^a	1.06	1.05	1.07
Number of renally-cleared drugs	<0.001 ^a	1.44	1.29	1.61
Diabetes	<0.001 ^a	1.51	1.30	1.76
Heart failure	0.001 ^a	1.38	1.13	1.69
Aged care setting	0.008 ^a	1.28	1.06	1.55
CI-Confidence interval, Exp(B)-Odds ratio				

Table 3.6 Correlates of inappropriate prescribing

Note: ^a All p-values < 0.05 statistically significant

3.5 Discussion

The presence of renal impairment in older people is often under-recognised, leading to incorrect dosing.¹⁵⁶ Our findings suggest that both aged care residents and community-dwelling older people were often prescribed renally-cleared medicines, outside of the recommended guidelines. Overall, 28.1% of the elderly patients (n=1135 out of 4035) who were prescribed a drug under review received at least one drug inappropriately based on their renal function.

Previous overseas studies have reported a rate of inappropriate dosing of renally-cleared drugs in elderly patients ranging from 12% to 43% in long-term care settings.^{9 10 12} About 43% of the elderly patients received at least one of 20 renally-cleared drugs inappropriately in a

cohort of 456 patients in four long-term care facilities in Canada.⁹ The drugs most frequently prescribed inappropriately were allopurinol, glyburide, ranitidine and metformin, and variables like age, weight, number of medications and the number of physicians prescribing in the facility were predictive for receiving an inappropriate prescription based on CrCl.⁹ About 12% of the patients had evidence of inappropriate prescribing of at least one of 21 renally-cleared drugs in a longitudinal study of 3804 elderly patients in 133 nursing homes in the USA and factors associated with potentially inappropriate prescribing were age older than 85 years, obesity and multiple comorbidities.¹⁰ In a cross sectional study by Rahimi et al, 50% of the patients were prescribed with renally-cleared drugs and 25% of them had at least one medication dosed incorrectly for renal function.¹² A recent study in aged care residents in Australia has recognised metformin and perindopril as the top most inappropriately prescribed drugs in aged care settings.¹⁴⁰

The most inappropriately prescribed medications identified in our study were perindopril, fenofibrate, olmesartan, gliptins, metformin, bisphosphonates and strontium. The inappropriate prescribing of oral hypoglycaemics, angiotensin receptor blockers (ARBs), angiotensin-converting-enzyme-inhibitors (ACEIs) and drugs for the treatment of bone diseases for elderly patients with renal impairment has been noted in various studies.^{9 11 133}

ACEIs and ARBs are recommended as first line therapy in diabetic kidney disease and non-diabetic kidney diseases with proteinuria.¹⁵⁷ In addition to lowering blood pressure, they have been found to reduce proteinuria and delay progression of CKD.¹⁵⁸ Benazepril therapy was associated with a reduction of 23% in the rate of decline in renal function and a 52% reduction in the level of proteinuria.¹⁵⁹ A lower dose of these agents is sufficient to treat hypertension in moderate to severe chronic renal impairment.^{160 161} but dose increment or use of maximum dose provides renoprotective benefits and slows CKD progression.¹⁶² However, it is worth noting that the very ACEIs used for its nephron-protective benefits may cause hyperkalemia, hypotension and acute decline in GFR of up to 15% from baseline.^{163 76}. An acute decline in GFR is not necessarily a reason to discontinue these drugs if the benefits outweigh the risk (particularly for those with severe congestive cardiac failure).¹¹⁵ A recent observational study has reported that discontinuing ACEIs and/or ARB in patients with advanced CKD (stages 4 & 5) who are progressing to complete kidney failure/renal replacement therapy results in stabilization and improvement of kidney function and decreases or delays the need for dialysis.¹¹⁵ A randomised controlled trial called “STOP-ACEI trial” designed to confirm the association between stopping these drugs and stabilisation of kidney

function is ongoing.¹⁶⁴ Till the further safety data emerge, it is ideal to withhold its use in general practice in patients with severe renal impairment. If used, patients should be monitored with extreme caution, as there is no sufficient evidence for safety. It is recommended that the renal function and electrolytes level be monitored while prescribing these drugs in patients with CKD as the decreased renal function affects the excretion of ACEIs and increases the risk of hyperkalaemia.^{38 157} The Kidney Health Australia and the Australian Medicine Handbook recommends stopping the usage of the ACEIs or ARBs, if the reduction in GFR exceeds 25% below the baseline value.^{38 43}

Bisphosphonates (alendronate and risedronate) are recommended as the first line therapy for prevention of osteoporotic fractures and are widely used for treatment of osteoporosis in post-menopausal women.¹⁶⁵ Manufacturers suggest avoiding their use in severe renal impairment. However, patients who are at risk of fracture or have osteoporosis are mainly elderly or post-menopausal women and may have age-related decline in renal function or chronic kidney disease (CKD). This creates a significant challenge for prescribers in managing osteoporosis in these high-risk patients. The prescribing restrictions of bisphosphonates in CKD were based on the assumptions that chronic use of these drugs lead to further decline in renal function and retention of bisphosphonates in the skeleton increases, resulting in “switch-off” of bone turnover.¹⁶⁶ However, there are no robust data in terms of both alteration in pharmacokinetics and the impact on skeletal histology with bisphosphonate treatment in patients with CKD.¹⁶⁶ A lack of strong scientific evidence and applicability of these recommendations in clinical settings have been recognised.^{167 168} On the one hand, there are reports describing adverse renal events, such as acute tubular necrosis and tubulointerstitial damage pertaining to bisphosphonates, while various studies have emphasised that bisphosphonates are safe even when there is a pronounced reduction in renal function.^{169 170 171-173} The number of randomised controlled trials conducted to guide renal dosing of bisphosphonates in CKD is limited. Furthermore, small sample sizes, short durations of treatment and the retrospective nature of these studies restrict the generalisation of their findings.¹⁷⁴ Larger, longer-term prospective studies on use of bisphosphonates in patients with CKD are warranted to ascertain the risks and benefits associated with these drugs in renal impairment.¹⁷⁴ However, until the results of new studies confirm the safety of bisphosphonates in renal impairment and the new guidelines for using bisphosphonates in elderly with renal impairment are put into routine clinical practice, the current prescribing information for bisphosphonates as mentioned in the product information or the standard drug information

sources, should be followed. The current prescribing information suggests withholding bisphosphates in patients with severe renal impairment and using reduced dose in mild to moderate renal impairment.

Another medication of particular interest was glibenclamide. It is well documented there is a high-risk of drug-induced hypoglycaemia associated with this drug if used in older people with renal impairment.^{175 176} The AMH recommends avoiding this drug in renal impairment and emphasises using glipizide or gliclazide.¹⁷⁷ In contrast, the manufacturers' product information recommends avoidance only in severe impairment and suggests using with caution in moderate impairment.¹⁷⁸

Our logistic regression analysis identified older age, presence of diabetes, heart failure, number of renally-cleared drugs (requiring dosage adjustment) prescribed and aged care setting to be associated with patients being prescribed one or more potentially inappropriate renally-cleared drugs. The mean age of the patients in the RMMR group was greater than that of the HMR group, however this was not statistically significant. Both the variables 'living in aged care facilities' and 'advancing age' were independently associated with patients being prescribed one or more renally-cleared drugs inappropriately, as evident in the multivariate model. Studies have shown that inappropriate prescribing of renally-cleared drugs is more likely to occur in older people.^{9 10} There is an age-related decline in renal function in older patients that warrants dose reduction or avoidance of renally-cleared drugs. This natural decline in renal function markedly affects the clearance of drugs, even in the absence of CKD. Advanced age and presence of renal impairment have been found to be the major pathophysiological factors not accounted for in drug dosing.¹⁷⁹

It is well known that polypharmacy is one of the contributing factors for potentially inappropriate prescribing in patients over 65 years.¹³⁰ In our analysis, we only looked at the occurrence of inappropriate prescribing (excessive dose or contraindicated with respect to CrCl) for drugs that are known to be problematic in older patients with declining renal function. We found that with more drugs (requiring dose adjustment) prescribed, the higher the likelihood of inappropriate dosing based on renal function.

Diabetes is the one of the most common diseases in elderly that contributes to the development of CKD.^{180 181} It has been recognised that comorbidities like diabetes increases the likelihood of receiving potentially inappropriate prescription in older people.¹⁴³ Patients with diabetes are at increased risk for receiving inappropriate dosing based on renal function.

Due to the fact that several drugs requiring dose adjustment are often prescribed in diabetes, and the disease itself is associated with renal impairment, patients with diabetes are at higher risk for inappropriate dosing based on renal function. CKD is associated with increased prevalence of heart failure, and, conversely, heart failure itself is a major contributor to CKD.¹⁸² Thus, many medications require dose modification in patients with heart failure, due to the associated decline in renal function. Therefore, it would be best to monitor the renal function while prescribing newer drugs, nephrotoxic drugs or renally-cleared drugs in patients with diabetes or heart failure.

A recent retrospective study in Australia examining RMMR reports from 911 aged care residents found that 48% of the residents had CKD and 16% of them received inappropriate prescription for renally-cleared medications.¹⁴⁰ Similarly, we also observed that inappropriate prescribing of renally-cleared medications was common among residents of aged care facilities and our analysis demonstrated that aged care residents were more likely to receive inappropriate prescribing based on renal function. This could be attributable to the fact that there was a higher prevalence of CKD in the aged care patients as reported by their lower mean for CrCl.

Designing an intervention program targeted toward improving the prescribing of these medications seems necessary. Computerised alerts at the time of electronic prescribing have been proven to be effective in improving dosing of primarily renally-cleared medications.¹⁸³ Other possible approaches for consideration would be conducting education/training programs for general practitioners and pharmacists geared towards recognising drugs that need caution in renal impairment as well as the patients at risk.

A limitation of this study is that we could not determine clinical outcomes, such as adverse drug events associated with the inappropriate prescribing. Also, we could not determine the outcome of the HMR and RMMR reports because the data were not available to us. Further, the prescribers might have used a different information source than the AMH for renal drug dosing. The conflicting recommendations for the renal dosing of renally-cleared drugs among the commonly used drug information sources have been recognised.¹⁷⁷ Also, CrCl could not be calculated on all patients due to lack of weight; thus, laboratory-based MDRD eGFR was used to identify inappropriate prescribing. Traditionally, the CrCl estimated from the Cockcroft Gault equation has been used for dosing purposes. However, the recent recommendations from the Kidney Health Australia, the National Kidney Disease Education Program (NKDEP), Food and Drug Administration (FDA) and the National Institute of

Diabetes and Digestive and Kidney Diseases (NIDDK) suggest that MDRD-based eGFR can be also be used for dosing of non-critical drugs in primary settings.^{87 103 184 185}

The eGFR reported in our study database were based on the MDRD formula. The medication review cases were collected prior to the adoption of the CKD-EPI formula by the Australian laboratories for reporting eGFR.¹⁰⁶ However, some of the ranges for renal functions were quite narrow and this together with the use of eGFR as a substitute for CrCl for some patients may have led to significant confounding in the study.

Our study was limited to drugs in the DVA list, so we excluded other renally important drugs used primarily in community settings such as antibiotics. This might have underestimated the extent of prevalence of inappropriate prescribing.

3.6 Conclusions

Potentially inappropriate prescribing of renally-cleared drugs is common in older Australians in community and aged care settings. Intervention studies to improve prescribing of renally-cleared drugs in the elderly appear warranted.

3.7 Next step

A key observation from the study above is that despite the existence of published guidelines for renal drug dosing, aged care residents and community dwelling older people are often prescribed renally-cleared medicines, outside of the recommended guidelines. Several explanations may be elucidated for this lack of dose adjustment. Prescribers' poor knowledge of medications requiring dosage adjustment, the presence of renal impairment being overlooked by prescribers, lack of routine measure of renal function, inadequate data on the information sources to guide the prescribers on precautions and renal dosage adjustments and confusion surrounding the use of renal function estimating equations are proposed contributing factors to inappropriate prescribing. In the following chapters, we will explore these factors. The nature and types of renal dosing recommendations available in the standard drug information sources will be examined to determine if there is both adequate information and consistency across the sources.

Chapter 4 DOSE ADJUSTMENT GUIDELINES FOR MEDICATIONS IN PATIENTS WITH RENAL IMPAIRMENT: HOW CONSISTENT ARE DRUG INFORMATION SOURCES?

4.1 Abstract

Background

It is known that patients with renal disease are often administered inappropriate dosages of drugs. A lack of quantitative data in the available drug information sources and inconsistency in dosing information may augment the problem of dosing error.

Aims

To determine the concordance among five drug information sources regarding the dosing recommendations provided for drugs considered problematic in patients with renal impairment and to determine the consistency among the sources regarding the definition of renal impairment and categorisation of chronic kidney disease.

Methods

Five standard drug information sources were reviewed for 61 drugs recommended to be used with caution in renal impairment. Information on recommendations for dosage adjustment in renal impairment was extracted and analysed. Further, the definition and classification of renal impairment were recorded. The recommendation for each drug was coded into six different categories and the inter-source reliability was calculated.

Results

Only slight agreement was observed among the sources (Fleiss Kappa: 0.3). Qualitative data were not well defined, and there was a lack of consistency in quantitative values. Some drugs marked as contraindicated in one source were not mentioned as such in others. Also, drugs considered as not requiring dosage adjustment in one source had explicit recommendations in other sources. The definition and classification of renal impairment differed among the five information sources.

Conclusions

There should be an evidence-based approach to drug dosage adjustment in order to bring uniformity to the recommendations. Regular updating of the content of the drug information sources is also important.

4.2 Introduction

Chronic kidney disease (CKD) is a long-term health condition where a person has reduced renal function, with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², lasting for 3 months or more.² The prevalence of CKD increases disproportionally in older people because of age-related physiological changes in renal function, alongside the increasing prevalence of other conditions such as diabetes and cardiovascular disease.^{146 186} Impaired renal function can have pronounced effects on the pharmacokinetics of many drugs as a result of alterations in glomerular filtration, tubular secretion, reabsorption or metabolism.⁸² Therefore, there is an increased risk of drug-related problems such as the use of contraindicated drugs and inappropriate doses, with potential adverse outcomes.^{187 188} It is essential to select the proper drug and individualise the dosage in order to avoid the occurrence of adverse events.¹⁴⁹ Previous studies have reported that 20–67% of prescriptions for patients with impaired renal function contain errors.^{9 13 15 189 190} The asymptomatic nature and opportunistic diagnosis of CKD are reasons for the higher prevalence of inappropriate prescribing.^{29 191} Other contributing factors reported include prescribers' poor knowledge of medications requiring dosage adjustment, the presence of renal impairment being overlooked by prescribers, underestimation of potential adverse events, and the lack of evidence-based data to guide prescribers on precautions and dosage adjustments.^{131 133 192} Moreover, a lack of quantitative data in the available drug information sources, and contradiction and inconsistency in dosing information may augment the problem of dosing error.¹⁹³ In Australia, the *Australian Medicines Handbook* (AMH)⁴³ or the product information, provide recommendations for dosage adjustment in renal impairment. Other international resources commonly accessible include the *British National Formulary* (BNF)¹²³ and the *American Hospital Formulary System* (AHFS).¹²⁵ However, despite their availability, significant practice gaps have been reported in prescribing for patients with renal impairment.

The purpose of this study was to compare systematically the recommendations for dosage adjustment in renal impairment among different drug information resources. We consulted the AMH (2012), Monthly Index of Medical Specialties (MIMS; 2012),¹²⁴ BNF (2012), AHFS (2012), and a specialised text, *Drug Prescribing in Renal Failure* (DPRF; 2007),⁸¹ for a range of drugs that are known to be problematic when used in patients with renal impairment. The specific objective was to determine the consistency among the sources in dosing recommendations provided for individual drugs and in the definition of renal impairment and categorisation of CKD.

4.3 Methods

This systematic comparison included data extracted for 61 drugs recommended as to be used with caution in patients with renal impairment by the Department of Veterans' Affairs, Australia¹⁰⁸. Recommendations for dose modification in renal impairment for each of the 61 drugs were extracted from the five sources. When a drug had more than one brand available in MIMS, only one brand was chosen randomly for analysis. Data extraction also included the definitions and categorisation of renal impairment in each of the five sources. One researcher (AK) extracted the data, which was reviewed independently by another researcher (RC). The definitions and categorisation of renal impairment reported in each of the five sources were compared to determine consistency. The recommendations for dose modification extracted from the five sources were allocated into six categories using an adaptation of the categorisation described by Vidal *et al.* as follows.¹⁹³

1 Contraindicated (CI): This category included drugs that were recommended to be avoided in renal impairment of any severity. For example, the AHFS recommended that 'metformin alone or in fixed combination with other drugs is contraindicated in renal impairment'.

2 Missing (M): This category included drugs that were not included in the information source. For example, AHFS contained no information on vildagliptin and strontium ranelate.

3 Numerical recommendations (N):

- Dose modification is recommended based on creatinine clearance (CrCl) calculated by Cockcroft-Gault (CG) formula or eGFR/serum creatinine (SCr) value. For example, AMH recommended a maximum daily dose of 50 mg for sitagliptin in patients with CrCl between 30 and 50 mL/min and 25 mg for patients with CrCl of less than 30 mL/min.
- Dose modification based on CrCl/eGFR/SCr is not mentioned, but there is a clear recommendation to avoid the drug below a certain range of CrCl/eGFR/SCr value.

For example, AMH recommended teriparatide to be avoided in patients having a CrCl below 30 mL/min.

4 Non-numerical recommendations (NN):

- *Recommendations that were ambiguous.* For example, the recommendation for metoclopramide in the BNF was to avoid or use small doses in severe renal impairment.
- *Did not mention the eGFR/CrCl value/severity of renal impairment for which the drug had to be avoided or reduced.* For example, the recommendation for topiramate in AMH included

‘reduced maintenance dose and longer interval between dose adjustments may be needed in renal impairment as it takes longer to reach steady state concentrations’. Further, phrases like ‘avoid in severe impairment’ in MIMS and AHFS were considered as non-numeric recommendations as these sources did not predefine ‘severe renal impairment’. However, if these sources mentioned the CrCl/eGFR range next to the severity of renal impairment, then such recommendations were considered to be numerical recommendations.

- *Use with caution.* The drug information sources mentioned one of the following statements but failed to give the specific recommendation for dose adjustment based on the CrCl/eGFR/SCr value: ‘careful monitoring of dose is required’, ‘monitor the drug serum concentration’ and ‘monitor for side effects’. For example, AHFS recommended that ‘particular attention to close monitoring of methotrexate is recommended for patients with renal impairment’.

- *Did not specify the required dose for the particular stage of renal impairment.* For example, the recommendation for enoxaparin in BNF was ‘risk of bleeding increased, reduce dose if eGFR less than 30 mL/min/1.73 m² – consult product literature for detail’.

5 No advice mentioned (X): The drug monograph was present in the information source, but there was no information on its use in patients with renal impairment. For example, the monograph for vardenafil in AMH contained no information regarding dose adjustment in patients with renal impairment.

6 Dosage adjustment not required (Y): The information source advised to give the normal drug dose in renal impairment. For example, the DPRF recommended that dose adjustment for bupropion is not required. For the purpose of analysis, the six categories of recommendations were coded numerically to assign computable values with CI = 1, M = 2, N = 3, NN = 4, X = 5 and Y = 6 respectively. The concordance in dosing recommendation for all 61 drugs among the different sources was calculated using Fleiss Kappa (K).¹⁹⁴⁻¹⁹⁶ Kappa value ranges from -1 to 1. Values ≤ 0 indicate poor agreement, 0.00–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 indicates almost perfect agreement. The concordance was determined in two approaches using REcal, an intercoder reliability web service.¹⁹⁷ In the first approach, concordance was calculated for the 34 drugs that had information in all five sources, excluding drugs that were missing from one or more sources. In the second analytical approach, the DPRF book was excluded, as it was an older publication, and the concordance was determined for the 54 drugs included in all the remaining four information sources.

4.4 Results

All the five information sources provided recommendations in quantitative terms for the majority of drugs examined in the study (Table 4.1).

Category	AMH	MIMS	BNF	AHFS	DPRF
Contraindicated (CI)	3	1	1	2	0
Missing (M)	0	0	1	6	27
Numeric (N)	48	41	47	37	30
Non-numeric (NN)	9	17	12	14	0
No advice (X)	1	0	0	1	0
Not required (Y)	0	2	0	1	4
Total drugs	61	61	61	61	61

Table 4.1 Category of renal dosing information in drug information sources

AHFS, American Hospital Formulary System; AMH, Australian Medicines Handbook; BNF, British National Formulary; DPRF, Drug Prescribing in Renal Failure; MIMS, Monthly Index of Medical Specialties.

AMH provided precise recommendations (N and CI) for the highest number of drugs ($n = 51$), followed by BNF ($n = 48$). Monographs for 44% of the drugs ($n = 27$) were missing from DPRF. However, DPRF generally provided the clearest information for the other drugs. The first analysis showed only slight agreement (K: 0.3) among the five information sources. A moderate agreement (K: 0.4) was observed in the second analysis when the DPRF was excluded. When assessing the individual categories of drugs, the least agreement was found among the recommendations for gliptins (K: -0.19), followed by genitourinary drugs (K: -0.05), angiotensin-converting enzyme (ACE) inhibitors (K: -0.03), oral hypoglycaemics (metformin, glimepiride, glibenclamide) (K: 0.04), musculoskeletal drugs (K: 0.15), psychotropic drugs (K: 0.19) and neurological drugs (K: 0.19). There was marked variation among the information sources in how they presented the contraindicated drugs. In various instances, drugs marked as contraindicated in one source were not mentioned as such in others (Table 4.2).

Drugs	AMH	MIMS	BNF	AHFS	DPRF
Glibenclamide	CI	NN	NN	CI	N
Codeine	CI	NN	NN	NN	N
Metformin	N	N	N	CI	N
Vardenafil	X	Y	N	Y	M
Candesartan	N	N	N	NN	Y
Alprazolam	NN	NN	NN	NN	Y
Bupropion	NN	NN	N	NN	Y
Hydromorphone	NN	NN	NN	NN	Y
Teriparatide	N	Y	N	X	M

Table 4.2 Discrepancies among the information sources

AHFS recommended avoiding metformin use even in mild renal impairment. However, the avoidance range for metformin according to AMH was $\text{CrCl} < 30 \text{ mL/min}$; for MIMS, it was $\text{CrCl} < 60 \text{ mL/min}$; for BNF, it was $\text{eGFR} < 30 \text{ mL/min}$; and for DPRF, it was $\text{GFR} < 10 \text{ mL/min}$. AMH and AHFS considered glibenclamide to be contraindicated in renal impairment, while DPRF recommended using normal dose in even severe renal impairment ($\text{GFR} < 10 \text{ mL/min}$). AMH considered codeine as contraindicated, whereas three information sources (MIMS, AHFS and BNF) did not specify this contraindication, and interestingly, DPRF recommended using half of the normal dose even if $\text{GFR} < 10 \text{ mL/min}$. Similarly, drugs that required no adjustment according to one source had explicit quantitative recommendations in other sources. There were seven such instances for six different drugs. Three drugs (candesartan, alprazolam, hydromorphone) for which DPRF recommended no adjustment required were categorised by other sources as requiring it. For vardenafil, the BNF recommended reduced dosage in patients with renal impairment, whereas MIMS and AHFS recommended that no dosage adjustment was required. While MIMS recommended no adjustment for teriparatide, AMH and BNF provided quantitative recommendations. Monographs for both vardenafil and teriparatide were missing from DPRF. Apart from the

dissimilarity in the categories of recommendation, disparity was found among the information sources in relating to how they provided the quantitative recommendation. The dose reduction and dosing frequency advised for the particular drugs in the varying severities of renal impairment, contrasted among the sources (Table 4.3)

On examining the individual information sources, it was found that some of the recommendations were contradictory. For instance, with regard to famotidine in AHFS, this information source suggested using one-half the normal dosage or prolonging the dosing interval to 36–48 h according to the patient's clinical response in moderate renal impairment ($\text{CrCl} < 50 \text{ mL/min}$) or severe impairment ($\text{CrCl} < 10 \text{ mL/min}$). On the other hand, the same information source advised to use one-half the usual adult dosage in adults with CrCl of 30–60 mL/min/1.48 m^2 of body surface area and use one-fourth the usual adult dosage in patients with $\text{CrCl} < 30 \text{ mL/min/1.48 m}^2$. Other examples were: metoclopramide in BNF, 'avoid or use small dose in severe renal impairment'; and bisoprolol in MIMS, 'no dosage adjustment is required in patients with impairment of the kidney because of excretion equally by both liver and kidney. Nevertheless, caution is advised' (Table 4.4).

Drugs/dose for normal renal function	AMH		MIMS		BNF		AHFS		DRIRF	
	<i>CrCl (mL/min)</i>	<i>Dose (Max/day)</i>	<i>CrCl (mL/min)</i>	<i>Dose (Max/day)</i>	<i>eGFR (mL/min/1.73 m²)</i>	<i>Dose (Max/day)</i>	<i>CrCl (mL/min)</i>	<i>Dose (Max/day)</i>	<i>GFR (mL/min)</i>	<i>Dose (Max/day)</i>
Metformin 500-850 mg bd	60-90	2 g	<60	Avoid	<45	Review the dose	Avoid in RI		>50	50
	30-60	1 g			<30	Avoid			10-50	25%
	<30	Avoid							<10	Avoid
Glibenclamide 1.25-20 mg q24h	RI	Avoid	Severe RI	Avoid	Use with care in mild to moderate RI Avoid where possible in severe RI	RI	Avoid	>50	No data	
								10-50	No data	
								<10	100%	
Sitagliptin 100 mg OD	30-50	50 mg	<60	Avoid	30-50	50 mg	30-50	50 mg	NA	
	<30	25 mg			<30	25 mg	<30	25 mg		
Saxagliptin 5 mg OD	<50	2.5 mg	>50	5 mg	2.5 mg in moderate to severe RI; use with caution in severe RI	>50	NR	NA		
			30-50	Avoid		≤50	2.5 mg			
			<30	Avoid		<30	Avoid			
Teriparatide 20 µg OD	<30	Avoid	Dosage adjustment not required		Caution in moderate RI; avoid if severe		No advice for dosage adjustment in RI		NA	
Bupropion 150-300 mg OD	RI: 150 mg		Use reduced dose and/or frequency		RI: 150 mg		Use with caution in RI		No need for dosage adjustment	
Duloxetine 30-60 mg OD	<30	30 mg OD	<30	30 mg	<30	Avoid	<30	Avoid	NA	

Table 4.3 Some examples of discrepancies in quantitative recommendations among the information sources

Note: RI: Renal impairment, ID: Initial Dose, MD: Maintenance Dose, ND: Normal Dose, NA: Not available, NR: Not required

Drugs	AMH	MIMS	BNF	AHFS
Analgesics	<p>Morphine: Use an alternative opioid (or reduce dose if CrCl <50 mL/minute).</p> <p>Hydromorphone: Reduce dose in renal impairment and monitor for adverse effects.</p>	<p>Tramadol: Avoid use or reduce dose.</p> <p>Codeine: Use with caution.</p> <p>Oxycodone: Dosage should be reduced and adjusted according to the clinical situation.</p>	<p>Morphine: Avoid use or reduce dose.</p> <p>Codeine: Avoid use or reduce dose.</p> <p>Hydromorphone: Avoid use or reduce dose.</p>	<p>Morphine: Use with caution.</p> <p>Codeine: Care should be exercised.</p> <p>Hydromorphone: Reduce initial dose.</p> <p>Oxycodone: Reduce dose and adjust according to the clinical situation.</p>
Neurological	<p>Baclofen: 5 mg initially; titrate dose cautiously according to response.</p> <p>Topiramate: Reduce maintenance dose.</p> <p>Levetiracetam: Reduce dose in renal impairment.</p>	<p>Topiramate: Renal clearance is decreased in renal impairment.</p>	<p>Topiramate: Use with caution if eGFR less than 60 mL/minute/1.73 m².</p>	<p>Baclofen: May be necessary to reduce either oral or intrathecal dosage in renal impairment.</p>
Psychotropic	<p>Lithium: Use reduced dose and monitor carefully.</p> <p>Bupropion: Use low dose and monitor for adverse effects.</p> <p>Benzodiazepines: Use a lower initial dose in severe impairment.</p>	<p>Lithium: Avoid in severe renal impairment.</p>	<p>Lithium: Avoid if possible or reduce dose.</p> <p>Bupropion: Reduce dose to 150 mg daily in renal impairment.</p>	<p>Lithium: Should not be used in patients with severe renal disease.</p> <p>Bupropion: Use with caution in patients with renal impairment.</p> <p>*Venlafaxine: Reduce dose by 25–50% in patients with mild-to-moderate renal impairment and by 50% in HD.</p>
Blood disorders	<p>Enoxaparin: Use with caution in renal impairment reduce dose if CrCl <30 mL/minute.</p>	–	<p>Enoxaparin: Reduce dose consult product literature.</p>	–

Musculo-skeletal	—	Methotrexate: Avoid in severe renal impairment. *Strontium ranelate: No dosage adjustment in patients with mild to moderate renal impairment. Avoid in severe impairment.	—	Methotrexate: Particular attention to close monitoring is recommended.
Cardio-vascular	Sotalol: Increase dosing interval. Seek specialist advice for dose adjustment in severe impairment. Bisoprolol: No dose reduction required up to 10 mg daily in renal impairment	Digoxin: Use with caution in renal impairment. Captopril: Initial daily dosage should be reduced Bisoprolol: No dosage adjustment is normally required up to the max dose of 10 mg.	Digoxin: Reduce dose and monitor plasma-digoxin concentration.	*Candesartan: 4 or 8 mg daily in severe impairment. Digoxin: Loading doses should be conservative. Spironolactone: Use with caution in renal impairment, contraindicated in rapidly deteriorating renal function, substantial impairment of renal excretory function.
Endocrine	—	—	Glimepiride: Should be used with care. Glibenclamide: Should be used with care.	Glimepiride: Initial dosing should be conservative.
Gastro-intestinal	—	Metoclopramide: Initiate therapy at half of the dose in patients with clinically significant degrees of renal impairment. Ranitidine: Reduce dose on severe renal impairment.	Metoclopramide: Avoid or use small dose in severe impairment.	—

Table 4.4 Examples of ambiguous recommendations in information sources

* Mild, moderate and severe impairment were not defined in the information sources.

CrCl was the most common index to direct the dosage adjustment in the information sources. AMH and DPRF recommended dose adjustment based on CrCl calculated by the CG formula. However, BNF provided recommendations based on eGFR calculated by the modification of diet in renal disease (MDRD) formula.¹⁹⁸ The renal function quantification methods varied among the drug monographs within AHFS and MIMS. For the majority of drugs, dosage adjustment was based on the CG formula, and for some drugs, the MDRD formula was used, especially when referring to manufacturers' recommendations. The definition and classification of renal impairment differed in all five sources. The classification for renal impairment in BNF categorised the renal function into five different stages; this complies with the definitions by the British Renal Association.¹⁹⁹ AMH had its own system of classification of renal impairment designed solely to aid the drug dosage adjustment; this differs from the *Caring Australians with Renal Impairment* guidelines.²⁶ DPRF defined renal impairment based on absolute GFR and divided them into three categories; this does not correspond to any standard classification system. MIMS and AHFS did not provide clear definitions of categories of renal impairment, and terms like mild, moderate and severe impairment were used without definition. Furthermore, various terms were used for dosage recommendation in the information sources without proper definition; these included a clinically significant degree of renal impairment, rapidly deteriorating renal function and substantial impairment of renal excretory function.

4.5 Discussion

There was considerable variation between the information sources in recommendations for the use and dosing of drugs in patients with renal impairment. Vidal *et al.* similarly concluded that there was poor consistency among four information sources: BNF, Martindale, AHFS and DPRF for the renal dosing of 100 drugs used commonly in the hospital setting.¹⁹³ However, their study had some limitations, particularly relating to the method of selecting the most commonly prescribed drugs within a hospital environment rather than focusing on high-risk drugs excreted primarily through the renal route.^{200 201} Therefore, we compared the drug information sources based on their dosing recommendations for the drugs that have most potential for inappropriate prescribing in kidney disease. The results of our study illustrate that there is a lack of quantitative recommendations in the various information sources to guide health professionals reliably on appropriate prescribing to minimise adverse outcomes in patients with renal impairment. It is recognised that it is unrealistic to quantify the appropriate

dose for some drugs with large pharmacodynamic variability— for instance, ACE inhibitors and β -blockers, whose dosage adjustment should not be based solely on pharmacokinetic parameters but clinical factors like blood pressure and heart rate as well. However, clear quantitative information in one source and unclear information in other information sources, such as ‘increase dosing interval’ or ‘seek specialist advice in severe impairment’, will complicate the prescribing decision. One of the reasons for the lack of robust dosing information could be the paucity of large population-based studies on dose adjustment in renal impairment. Another contributing factor could be the practice of the drug regulatory authorities that focuses mainly on clinical trials determining the maximum tolerated dosage in healthy, young individuals.²⁰¹ Keeping aside the fact that few studies are available that determine the correct dose in renal impairment, the dissimilarity between standard information sources regarding the reported availability of clinical study data was remarkable; drugs for which one information source mentioned a lack of clinical study data on dose adjustment, other sources provided clear quantitative recommendations. It is well understood that contraindications and cautions are seldom absolute, but the differing recommendations create ambiguity and uncertainty, and can misdirect the users or prescribers. For particular drugs, such as oral hypoglycaemics, H₂ receptor blockers, metoclopramide and many cardiovascular drugs, the information sources often did not provide explicit information for dosage adjustment, yet studies have shown that incorrect dosage adjustments are common with these categories of drugs.^{133 136} Guidelines for dose adjustment in renal impairment, even for drugs with a narrow therapeutic index (e.g. digoxin and lithium), were poorly mentioned in the information sources. Instead of a clear quantitative recommendation, qualitative and ambiguous terms like ‘reduce the dose’ and ‘loading dose should be conservative’ were often used. It was found that the information sources were relatively consistent in providing recommendations for newer drugs, such as levetiracetam, memantine, paliperidone, pramipexole and pregabalin. This improved consistency could be due to the manufacturers providing more robust data for clinical use and dosage adjustment, and regulatory authorities demanding more consistent information. Clearly, regular updating of the drug information sources is necessary, along with a need for all drugs that are to be used in patients with renal dysfunction to undergo at least one pharmacokinetic study in patients with varying degrees of renal impairment prior to marketing. An emphasis should be placed on conducting and disseminating research work focused on determining the correct drug dosage based on renal function. Uniformity in the categorisation of renal impairment would be desirable as prescribers tend to refer to more than one information source for advice on drug dose adjustment in renal impairment.²⁰² Keeping in mind the new practice

of automatic eGFR reporting, drug dosage recommendations based only on CrCl could be inconvenient.^{203 204} Recently, it was suggested that the method of calculating eGFR should be changed to the CKD Epidemiology Collaboration (CKD-EPI) formula and that all laboratories should report eGFR values as a precise figure to at least 90 mL/min/1.73 m².¹⁰³ However, it has been recommended that the dosage adjustment for drugs with a narrow therapeutic index or excreted primarily by the kidney should be guided by CrCl calculated by the CG equation.²⁰⁵ Further, in elderly or frail patients and in those with a low body mass index, CrCl is the preferred renal function quantification method.²⁰⁶ Therefore, recommendations for dose adjustment based on both CrCl and eGFR/CKD-EPI would be ideal. Editors of secondary sources accept the difficulties in finding and compiling the relevant information for patients with renal disease on which clear dosing guidelines can be formulated.^{201 207 208} Furthermore, the value of the product information will always be limited by the regulatory process (data requirements, economics and approval delays) and the generally conservative approach by manufacturers (fear of litigation). It will always be necessary to interpret the product information and make a risk-benefit decision for individual patients. Also, while adjusting the dose in clinical practice, the prescriber needs to be confident that the pharmacokinetic parameters of the patient they are treating do not vastly differ from the population in which the renal pharmacokinetic study was undertaken. Our study was limited to drugs used commonly in the community setting, and so excluded renally important drugs used primarily in hospital settings (e.g. aminoglycoside antibiotics). However, in light of the inconsistency in the recommendations for the 61 drugs in our study, we believe a similar result would be obtained if a greater number of renally problematic drugs were examined. Also, we acknowledge that there are other sources of drug dosing information in renal disease that might be used in practice, especially within specialist renal units. However, we have examined the information sources most commonly used by Australian general practitioners and pharmacists in the community setting.

4.6 Conclusion

There should be an evidence-based approach to drug dosage adjustment in renal disease to bring uniformity to the recommendations. Further, it would be beneficial to standardise the renal function quantification methods in the drug information sources. We believe that this would reduce the possibility of inappropriate dosing for patients with renal impairment.

4.7 Next step

This chapter provided evidence that there is considerable variation amongst the information sources in recommendations for dosing of drugs in patients with renal impairment. The standard drug information sources are a compilation of the data from the drug clinical trials and the PI is the archive of the pharmacokinetics results provided by the manufacturers. In the next step, we aim to review the product information for drugs that are recommended to be either avoided or used with caution in renal impairment and investigate the extent to which information is available on dosing in renal impairment and the concordance in recommendations between manufacturers' PI for the same generic drug.

Chapter 5 RENAL DRUG DOSING RECOMMENDATION: EVALUATION OF PRODUCT INFORMATION FOR BRANDS OF THE SAME DRUG

5.1 Abstract

We reviewed the official product information (PI) for brands of 28 drugs recommended to be either avoided or used with caution in patients with renal impairment, and investigated the extent to which information was available on dosing in renal impairment and the concordance between the dosing recommendations for the same generic drug. There was generally a lack of detailed information in the PI on the use of drugs in patients with renal impairment. The recommendations varied significantly among different brands of hydromorphone, morphine, oxycodone, tramadol, metformin and topiramate.

5.2 Introduction

Given the ageing of the population and the rising prevalence of chronic kidney disease (CKD), the quality of prescribing in patients with renal impairment is becoming increasingly important.^{85 209} Impaired renal function can be associated with alterations in drug absorption, protein binding, metabolism and excretion; therefore, it is essential to individualise the dosage of many drugs in order to avoid toxicity and the risk of therapeutic failure.^{82 149} The renal function of the patient should be considered when prescribing drugs that are eliminated unchanged by the kidneys, particularly those (i) with a narrow therapeutic index, (ii) with active metabolites that are primarily excreted by the kidney or (iii) that are nephrotoxic. The need for dosage adjustment can be determined by measurement of the kidney function of the patient, and the optimal dose can be determined by consulting standard drug information sources or the manufacturer's product information (PI), which has been approved by the Australian Therapeutic Goods Administration (TGA).

The Monthly Index of Medical Specialities (MIMS), a compendium of PI, is one of the most frequently consulted drug information sources in Australia.²¹⁰ However, it has been criticised for having out-dated information and inaccuracies in the listed PI.²¹¹ A review of PI in MIMS revealed the presence of numerous errors and potentially hazardous information pertaining to the management of poisoning.²¹² Similarly, a comprehensive assessment of MIMS to examine the extent to which paediatric dosing information is available in PI showed that 81% contained inadequate information.²¹³ In addition, marked discrepancies in paediatric dosing information between generic equivalent products were observed.

No formal studies in Australia have examined the renal dosing information in approved PI. Therefore, we aimed to review the PI for drugs that are recommended to be either avoided or used with caution in renal impairment,²¹⁴ and investigate the extent to which information is available on dosing in renal impairment and the concordance in recommendations between manufacturers' PI for the same generic drug.

5.3 Methodology

eMIMS²¹⁵ was examined for commonly used generic drugs (n=28) recommended by the Australian Department of Veterans Affairs (DVA) to be either avoided or used with caution in patients with renal impairment.²¹⁴ For each generic drug, all available brands, which were listed as having solid oral dosage forms were recorded. A total of 228 brands were obtained for the 28 drugs, corresponding to 30 manufacturers. One drug (digoxin) was excluded as the available brands were from the same manufacturer. In instances where a manufacturer had multiple brands for the same generics, only one brand was selected randomly. The final list of products included a total of 155 brands corresponding to 27 generic drugs. For each identified brand, the PI was consulted and data referring to renal impairment was collated from various sections: pharmacokinetics, contraindications, precautions, and dosage and administration. The renal dosing information within PI was assigned to one of four categories (Table 5.1). The dissimilarity between the PI from various manufacturers regarding the dosage recommendations was determined. Also, the use of CKD terminology and classification of renal impairment were recorded.

5.4 Results

There was generally a lack of detailed information in the PI on the use of drugs in patients with renal impairment. The majority of PI documents (88 of 155 PI; 57%) provided quantitative recommendations (Table 5.2) regarding dosage adjustments for renal impairment, but this was often not detailed enough to help users to make an informed decision. For instance, statements such as “avoid in severe renal impairment (creatinine clearance, CrCl<15 mL/min) but reduce dose and monitor side effects in moderate and mild impairment” were considered quantitative, but the recommendations are probably inadequate to perform dosage adjustment in patient care settings. For 37 PI documents (24%), an altered dosage regimen was proposed without a quantifiable measure of renal function reported in the dose recommendation. The

results of pharmacokinetic studies in patients with renal impairment were not presented in 59 PI (38%). Twenty brands did not have full PI and advice like “contact the manufacturer” was mentioned. Four of the PI mentioned the lack of data regarding use in patients with renal impairment and thus recommended avoiding the drug in these patients. The PI for relatively new drugs, such as levetiracetam, gabapentin and pramipexole, had more detailed renal dosing information than for older drugs.

<p>1. Quantitative</p> <ul style="list-style-type: none"> – Dose modification was recommended based on renal function value. – Clear recommendation to avoid the drug below a certain range of renal function. <p>2. Qualitative</p> <ul style="list-style-type: none"> – Ambiguous or imprecise recommendation. – Recommended altering the dosage regimen but did not provide any quantifiable dose based on renal function. <p>3. Contact manufacturer</p> <ul style="list-style-type: none"> – No PI provided in MIMS for the brands. – Advice such as “contact manufacturer for full prescribing information” was given. <p>4. Lack of data:</p> <ul style="list-style-type: none"> – PI implied that safety and effectiveness of product in renal impairment had not been established; therefore, avoid using the drug in severe renal impairment.
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Table 5.1 Types of renal dosing recommendations

Drug class	Generics	Number of PI examined	Nature of dosing information in PI			
			Contact manufacturer	Qualitative	Quantitative	Lack of data
Analgesics	Hydromorphone	2	-	2	-	-
	Morphine	3	-	3	-	-
	Oxycodone*	2	-	1	1	-
	Tramadol	10	2	3	5	-
Endocrine	Glibenclamide	2	-	2	-	-
	Glimepiride	7	1	1	5	-
	Metformin	10	1	1	8	-
Neurological	Baclofen	4	-	4	-	-
	Gabapentin	9	-	-	9	-
	Galantamine	4	-	-	4	-
	Levetiracetam	10	3	-	7	-
	Memantine	3	-	-	3	-
	Pramipexole	2	1	-	1	-
	Topiramate	8	1	-	7	-
Psychotropic	Amisulpride	4	-	-	4	-
	Alprazolam	6	-	6	-	-
	Bupropion	2	-	-	-	2
	Lithium	2	-	-	-	2
	Venlafaxine	8	2	-	6	-

Cardiovascular	Enalapril	9	2	-	7	-
	Atenolol	10	2	-	8	-
	Bisoprolol	9	1	8	-	-
	Digoxin**	-	-	-	-	-
	Spironolactone	2	-	-	2	-
Gastrointestinal	Ranitidine	11	3	8	-	-
Musculoskeletal	Allopurinol	4	-	4	-	-
	Alendronate	10	1	-	9	-
	Colchicine	2	-	-	2	-

Table 5.2 Nature of dosing information in product information from various manufacturers for the same generic drugs

*Available brands were in different formulation (conventional and modified release tablets), **excluded as both brands were from same manufacturer.

Sometimes, contradictory information was presented within the same PI. For instance, with *Memanza* (memantine), in the “contraindication section” of the PI, it is mentioned that the drug should not be used in patients with CrCl less than or equal to 50 mL/min. However, in the “dosage and administration section”, it is stated that in patients with moderate renal impairment (CrCl 30 - 49 mL/min) or severe renal impairment (CrCl 5 - 29 mL/min), the dose should be 10 mg per day.

The renal function severity terms used and the associated quantitative values were not consistent among the PI. The most common renal function measure reported in the PI was CrCl (77 of 155 PI). Few PI used explicit terms to define the severity of impairment but these were not consistent with the contemporary standard definitions of CKD. The recommendations for dosage adjustment in renal impairment varied among the PI for the different brands of six generic drugs out of 27 drugs examined. These drugs were hydromorphone, morphine, oxycodone, tramadol, metformin and topiramate (Table 5.3). The renal function severity at which the drug should be avoided varied among the PI. For instance, with tramadol, the avoidance range for the brand *Tramedo* was CrCl<10 mL/min whereas for the brand *Duotram* it was CrCl<30 mL/min. For the same drug, some brand’s PI provided ambiguous recommendations while other PI documents provided clear quantitative recommendations. For example, the brand *APO-Topiramate* recommended use with caution in patients with renal disease whereas the brand *Topamax* suggested using half of the usual starting and maintenance dose in moderate and severe renal impairment. Similarly, the renal function quantification method used in recommendations varied among the PI. For metformin, the brand *Glucophage* gave a dosage recommendation based on CrCl, whereas the brand *Genepharm* gave it with serum creatinine (SrCr).

Drugs	Brands/ Date of TGA approved information	Recommendation in PI	
		CrCl mL/min	Dose Max/day
Hydromorphone	Dilaudid 22/02/2010	Should be used with caution and the initial dose should be reduced in those with RI.	
	Jurnista 12/03/2013	Reduce dose in moderate renal insufficiency. In severe renal insufficiency reduce both dose and dosing interval and monitor for ADE.	
Morphine	Anamorph 7/05/2003	CI in severe renal disease.	
	Apotex 15/06/2011	CI in severe RI or use one-half the usual dose in significantly decreased renal function.	
Oxycodone	Endone 2/07/2009	In RI reduce dose and adjust according to clinical situation.	
	Oxycontin 3/11/2011	<60	one half of usual dose in RI
Tramadol	Tramal 5/04/2013	Not recommended in severe renal insufficiency.	
	APO-tramadol SR (south cross) 9/11/2010	<10	CI
	Dutrotram XR	<30	CI

	1/05/2008		
	GA tramadol SR	<30	Reduce dose
	28/05/2010	<10	Not recommended
	Lodam SR	Contact manufacturer	
	Tramedo SR	<30	Increase dosage interval to 12 hours
	8/02/2008	<10	CI
Metformin	Glucophage	<60	CI
	23/03/2012		
	Formet	Should not be used in diminished renal function.	
	16/06/2005		
	Metformin	CI in SrCr level> 135 micromols/L in males and > 110 micromols/L in females.	
	(Genepharm) 15/12/2005		
	Metformin Pfizer	Contact manufacturer.	
Topiramate	Topamax	Use half of the usual starting and maintenance dose in moderate and severe renal impairment.	
	14/08/2012		
	Topiramate Generic health	Contact manufacturer.	
	APO- Topiramate	Use caution in renal disease.	
	29/08/2012		

Table 5.3 Discrepancies among the various brand's product information on how they present the renal dosing information

5.5 Discussion

We found a lack of detailed information in the PI on the use of drugs in patients with renal impairment. The renal function severity terms used and the associated quantitative values were not consistent among the PI. The findings of our study are in concordance with the results of several overseas studies that concluded that there were inadequate dosage recommendations and marked discrepancies among the PI regarding the method to quantify renal function.^{216 217} We examined the eMIMS for drugs which have the most potential for adverse outcomes if prescribed inappropriately in renal impairment.¹¹ Therefore, we anticipated specific dosing recommendations based on the degree of renal impairment, as the dose information is of utmost importance in using these drugs safely and effectively in patients with renal impairment. However, we found that 38% of PI lacked data on pharmacokinetic studies in renal impairment and 24% suggested an altered dosage regimen without a quantifiable measure of renal function. Perhaps the provision of more complete pharmacokinetic data in special groups, such as those with renal impairment, should be compulsory for the registration of new drugs. In an attempt to improve the quality of renal dosing information, the United States Food and Drug Administration in 1998 published a “Guidance for industry: pharmacokinetics in patients with impaired renal function”.²¹⁸ The positive impact of this guidance on the consistency, clarity and quality of recommendations has been studied.²¹⁶ In Europe, the European Medicines Evaluation Agency published its “Note for guidance on evaluation of pharmacokinetics of medicinal products in patients with impaired renal function”.²¹⁹ This guidance was adopted by the TGA in Australia in 2004 to ensure that manufacturers give appropriate and specific dosage recommendations in patients with reduced renal function.²²⁰ Although the majority of PI examined here (85%) were recorded as having been approved by TGA in the post-guidance era, the consistency and quality of renal dosing recommendations were still questionable. The renal function severity values were also not uniformly consistent with the definition and range of renal function as recommended in the guidance.²²⁰

Dosage adjustment recommendations based on serum creatinine in the PI can be problematic as the serum creatinine is not a reliable marker of CKD.²²¹ Furthermore, the lack of prescribing information for some brands in eMIMS and impractical recommendations, such as contacting the manufacturer, might deter prescribers from dose adjustment or even using the information source. Also, the inconsistencies in renal dosing information between the PI from various manufacturers for the same generic drug is of concern and may have clinical

ramifications in patients with renal impairment, especially when the discrepancy is as marked as that mentioned above for tramadol.

The PI for older medicines often provided inadequate and out-dated recommendation for dose adjustment. Yet, a search of the literature revealed clear dose recommendations based on renal function for many of these drugs, including baclofen, ranitidine, oxycodone and topiramate.^{165 222-225} Clearly, regular updating of the PI seems necessary. Perhaps, an expiry date should be assigned for PIs in order to enforce upgrading the information with time. Otherwise, in clinical practice prescribers perhaps know that the PIs are often out of date and tend to ignore them - either using therapeutic drug monitoring, if available, or clinically monitoring the patients.

A recent study found conflicting recommendations for the renal dosing of medications among PI and four other commonly used drug information sources.¹⁷⁷ The limited updating of PI in MIMS has been highlighted previously. A detailed critique of PI for thyroid medications from four different manufactures pointed out erroneous therapeutic recommendations, inappropriate dosage adjustment and exclusion of well recognised indications and side effects.²¹¹ It was observed that 11 of 16 errors remained uncorrected two years after the publication of this review.²²⁶ On examining the PI after six years, it was found that the errors still remained uncorrected.²²⁷

5.6 Conclusion

There were inconsistent or missing renal drug dosing recommendations across brands for the same generic drug. Regularly updating of PI seems necessary. The measure of renal function also requires standardisation to ensure optimal drug dosing.

5.7 Next step

This chapter demonstrates that inconsistent or missing renal drug dosing recommendations across brands for the same generic drug remains a significant problem. Lack of information to guide the prescribers on precautions and dosage adjustments contributes to inappropriate prescribing leading to adverse outcomes in patients with renal impairment. The inconsistency in renal function severity terms used and the associated quantitative values among the PI create ambiguity and uncertainty, and can misdirect the users or prescribers. This adversely affects the quality of prescribing and should be considered as a factor contributing to inappropriate prescribing. By regularly updating the PI and bringing standardisation in the measure of renal function, better outcomes may be achieved for improving usage of medicine and quality of care for CKD patients as whole.

In the next step, we are examining another important factor that contributes to inappropriate prescribing in patients with renal impairment. An essential part of the safe drug prescribing in patients with CKD is the accurate estimation of renal function as CKD staging influences all aspects of pharmacological and non-pharmacological therapy, especially in identifying the drugs that need to be avoided or require dose modification.

The agreement among the renal function estimating equations in dosing of renally-cleared drugs commonly prescribed in primary care settings, is an important issue to be addressed in improving usage of medicine in CKD patients.

Chapter 6 COMPARISON OF EQUATIONS FOR DOSING OF MEDICATIONS IN RENAL IMPAIRMENT

6.1 Abstract

Aim: To determine the concordance among the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) and the CKD-Epidemiology Collaboration (CKD-EPI) equations in hypothetical dosing of renally-cleared medications.

Methods: A total of 2163 patients prescribed at least one of the 31 renally-cleared drugs under review were included in the study. Kidney function was estimated using the three equations. We compared actual prescribed dosages of the same drug to recommended dosages based on the kidney function as calculated by each of the equations and applying dosing recommendations in the Australian Medicines Handbook.

Results: There was a significant difference in the kidney function values estimated from the three equations ($P < 0.001$). Despite the good overall agreement in renal drug dosing, we found selected but potentially important discrepancies among the doses rendered from the equations. The CKD-EPI equation non-normalised for body surface area had a greater rate of concordance with the Cockcroft-Gault equation than the MDRD equation for renal drug dosing.

Conclusions: There is need for a long-term multi-centre study in a diverse population to define the clinical effects of the discrepancies among the equations for drug dosing. Given the greater concordance of the non-normalised CKD-EPI equation with the Cockcroft-Gault equation for dosing, the recommendation by Kidney Health Australia and the United States National Kidney Disease Education Program that “dosing based on either eCrCl or an eGFR with body surface area normalisation removed are acceptable” seems suitable and practicable for the purpose of dosing of non-critical drugs in the primary care setting.

6.2 Introduction

Chronic kidney disease (CKD) is a significant and growing public health problem that is associated with premature mortality.²⁷ Renal impairment alters the effects of many drugs, sometimes decreasing their effects but more often increasing their effects and potentially toxicity.¹⁰⁷ Many of these changes are predictable and can be prevented by adjusting drug doses.⁷⁶ Traditionally, the creatinine clearance (CrCl) estimated by the Cockcroft-Gault equation⁹³ has been the most commonly used method to estimate renal function for drug dosing purposes, as evidenced by its widespread use in both drug developmental arenas and recommendations that appear in pharmaceutical product information.⁹³ In recent years, several new equations have been proposed to estimate kidney function in patients with CKD; the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equations.^{97 102} These latter equations, normalised for the patient's body surface area (BSA) and expressed in mL/min/1.73 m², are routinely used in Australian laboratories and health centres to automatically report eGFR with every request for serum creatinine determination.^{203 204} There is abundant evidence that these two new equations provide more accurate estimation of the GFR.⁹⁸ However, there has also been discussion on whether these new equations could be used for renal drug dosing.²²⁸⁻²³¹ Studies have questioned the use of the Cockcroft-Gault equation for renal dosing and recommended using MDRD for conducting renal pharmacokinetic studies and adjusting doses in the clinical settings.^{87 185} The Cockcroft-Gault formula is prone to high variability due to inconsistent use of ideal, actual or adjusted body weight, and indicates the need for dosage adjustment more often due to a more conservative estimation of kidney function.^{232 233}

The United States National Kidney Disease Education Program stated that either the Cockcroft-Gault or MDRD equation can be used as the estimate of kidney function for drug dosing.²³⁴ Similarly, in 2007 the Australasian Creatinine Consensus suggested that using the eGFR calculated with the MDRD formula was acceptable to assist with drug dosing decisions in general practice for non-critical-dose drugs.¹⁰³ This has led to considerable debate on the topic^{231 235} with some studies suggesting that Cockcroft-Gault should remain the equation of choice for drug dosing as the differences in the doses rendered were too significant to replace Cockcroft-Gault with MDRD for dosing.^{217 231 236-239}

The CKD-EPI equation has been recommended to be used in clinical laboratories to routinely provide eGFR values with each request for serum creatinine.¹⁰⁶ There is, however, limited information on the clinical application of this equation for the purpose of dose

adjustment. Further, unlike MDRD, there has been no formal recommendation on use of this equation for drug dosing. However, it is worth noting that clinicians often use the eGFR provided by the laboratories for drug dosing purposes in the clinical setting.²⁴⁰

Given this background, we were interested to evaluate the agreement among the three formulae if hypothetically used in dosing of renally-cleared drugs commonly prescribed in primary care settings. The two objectives of the study were (1) compare kidney function estimates based on the CKD-EPI, Cockcroft-Gault and MDRD equations, and 2) determine the concordance among the Cockcroft-Gault equation, MDRD (with and without BSA normalisation) and the CKD-EPI equation (with and without BSA normalisation) for hypothetical dosing of renally-cleared medications.

6.3 Methods

We examined a sample of de-identified medication review cases extracted from the database of Medscope, an IT company providing decision support solutions for accredited pharmacists performing medication reviews. The Home Medicines Review and Residential Medication Management Review services were conducted by accredited pharmacists in collaboration with GPs between January 2010 and June 2012. Methods for data extraction for this study have been explained previously.²⁴¹ Ethical approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee (H0012386).

All individuals (n=2163) who had their weight, height and serum creatinine reported and were prescribed one or more of the drugs under review, were included in the study. We used a list of 31 renally-cleared drugs that are commonly prescribed in the community and recommended, by the Australian Department of Veterans' Affairs, to be avoided or used with dose adjustment in patients with renal impairment (Appendix 1).²⁴²

Kidney function was estimated using the MDRD, CKD-EPI and Cockcroft-Gault equations. The CrCl was estimated using actual body weight, as we aimed to compare the Cockcroft-Gault equation; based on actual body weight with the MDRD and CKD-EPI equations both with and without normalisation for body surface area. The estimated kidney functions were analysed for any significant discrepancies (Table 6.1). To further elucidate the impact of the observed discrepancies on drug dosing, for each patient we compared actual prescribed dosages of the same drug to recommended dosages based on the level of kidney function as calculated by each of the estimating equations and applying explicit

recommendations for renal drug dosing in the Australian Medicines Handbook (AMH).⁴³ For each drug, the prescribed doses were marked as ‘appropriate (A)’, ‘inappropriate (IA)’, ‘dose modification not required (NR)’ based on the conformity with the adjustment specified in the AMH using the kidney function estimated from each equation. Both inappropriately high dose and contraindicated prescription were treated as inappropriate prescription. Fleiss Kappa values along with pairwise percentage agreement were calculated to determine the concordance among the three equations.

CKD-EPI equation	<i>For females with $SCr \leq 62 \mu\text{mol/L}$</i>	$= 144 \times (SCr \text{ in } \mu\text{mol/L} \times 0.0113/0.7)^{-0.329} \times (0.993)^{\text{age in years}}$
	<i>For females with $SCr > 62 \mu\text{mol/L}$</i>	$= 144 \times (SCr \text{ in } \mu\text{mol/L} \times 0.0113/0.7)^{-1.209} \times (0.993)^{\text{age in years}}$
	<i>For males with $SCr \leq 80 \mu\text{mol/L}$</i>	$= 141 \times (SCr \text{ in } \mu\text{mol/L} \times 0.0113/0.9)^{-0.411} \times (0.993)^{\text{age in years}}$
	<i>For males with $SCr > 80 \mu\text{mol/L}$</i>	$= 141 \times (SCr \text{ in } \mu\text{mol/L} \times 0.0113/0.9)^{-1.209} \times (0.993)^{\text{age in years}}$
MDRD equation	$eGFR\text{-MDRD (mL/min/1.73m}^2) = 175 \times (SrCr \times 0.0113)^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ if female})$	
Cockcroft-Gault	$CrCl \text{ (mL/min)} = [(140 - \text{Age}) \times wt] / (0.813 \times SrCr) (\times 0.85 \text{ if female})$	

Table 6.1 List of GFR estimating equations

Units for all formulae. Serum creatinine concentration (SrCr) in $\mu\text{mol/L}$; Weight (Wt) in kg; Age in years

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; MDRD Study, Modification of Diet in Renal Disease Study

The Cockcroft-Gault equation is reported unadjusted for body surface area in units of mL/min, whereas MDRD and CKD-EPI equations are adjusted for body surface area. The recommended unit for drug dosing recommended by the Kidney Health Australia is mL/min. Also, the Therapeutic Goods Administration (TGA) approved product information provides dosing information by mL/min. Therefore, for the purpose of comparison, the GFR estimated using

MDRD and CKD-EPI were converted to this unit, by multiplying each patient's BSA and dividing by 1.73 m² and the analyses were repeated.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp., Excel 2010 (Microsoft Corporation, Redmond, USA) and ReCal online web service.¹⁹⁷ The analysis of variance (ANOVA) repeated measure test was used to determine the significance of differences in the kidney function estimates determined from the three equations (Cockcroft-Gault, MDRD and CKD-EPI). A P-value of less than 0.05 was considered as significant. The concordance in dosing recommendation for each drug based on the kidney function estimates from these equations was determined using Fleiss Kappa (K). Fleiss kappa is a statistical measure that calculates the reliability of agreement between more than two raters. It is a measure of the degree of agreement that can be expected above chance.¹⁹⁶

6.4 Results

The clinical characteristics of the study participants are summarised in Table 6.2. The mean age of the patients was 72.2 years and 59.5% were female. The ANOVA repeated measure test demonstrated a statistically significant difference in the kidney function values rendered from the three equations ($P < 0.001$). All pairwise comparisons between the values for eGFR and eCrCl were significantly different from each other ($P < 0.001$).

Characteristics	Mean (SD) or %
Age, years	72.2 (11) Range, 26:99
≥65	84.3
Female	59.5
Weight (kg)	80.7 (20.9)
Height (cm)	163.6 (10.2)
SrCr (μmol/L)	91.2 (40.3)
BMI, kg/m ²	30 (7)
>30 kg/m ²	45.1
BSA, m ²	1.9 (0.27)
Cockcroft-Gault (mL/min)	73.5 (38.9)
MDRD eGFR (mL/min/1.73 m ²)	71.8 (25.4)
CKD-EPI eGFR (mL/min/1.73 m ²)	66.2 (21.2)

Table 6.2 Patient Characteristics

Note: values expressed as mean (standard deviation) Abbreviations: BSA- body surface area, BMI-body mass index CG, Cockcroft-gault equation using actual body weight; MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI Chronic Kidney Disease – Epidemiology Collaboration

Table 6.3 shows the concordance among the three equations in dosing of the renally-cleared drugs. The level of agreement ranged from moderate to very good. Concordance among the equations was lower for drugs that have fewer kidney function categories for dose adjustment. When the analyses were repeated for the CKD-EPI and MDRD study equations with the removal of BSA normalisation (expressed in units of mL/min), a higher concordance was observed among the three equations (Table 6.3). Both the CKD-EPI and MDRD with the removal of BSA normalisation showed greater concordance to the Cockcroft-Gault equation than the normalised equations.

Table 6.4 shows the pair-wise comparison of the MDRD and the CKD-EPI equations with the standard Cockcroft-Gault. In comparison to the MDRD equation, the CKD-EPI equation had a greater concordance with the Cockcroft-Gault equation for renal drug dosing. This pattern was consistent with all the drugs tested.

At an individual level the discordance in the doses rendered from the equations was considerable. For each drug, the number of patients who required dosage adjustment or were prescribed doses higher than the recommended dose differed depending upon the equation used

to estimate renal function (Table 6.5). For instance, 39.5% and 38.8% of the patients receiving metformin would require dose adjustment if Cockcroft-Gault and CKD-EPI equations were used, respectively, to estimate the kidney function. However, 52.4% of the patients would require dosage adjustment based on the MDRD equation.

Drug/Dosing Level	N received this dose	Cockcroft-Gault (mL/min)			MDRD (mL/min/1.73 m²)			MDRD* (mL/min)			CKD-EPI (mL/min/1.73 m²)			CKD-EPI* (mL/min)			Overall agreement (Fleiss Kappa)	
		NR	IA	A	NR	IA	A	NR	IA	A	NR	IA	A	NR	IA	A	CG vs MDRD vs CKD-EPI	CG vs MDRD* vs CKD-EPI*
Dosing Level (1)																		
Alendronate	253	219	34	-	244	9	-	242	11	-	238	15	-	236	17	-	0.51	0.60
Risedronate	201	186	15	-	199	2	-	195	6	-	194	7	-	192	9	-	0.33	0.62
Strontium	69	61	8	-	67	2	-	66	3	-	67	2	-	66	3	-	0.46	0.61
Duloxetine	74	68	4	2	71	2	1	72	2	-	70	3	1	70	3	1	0.75	0.62
Dosing Level (2)																		
Sitagliptin	126	94	22	10	103	14	9	105	12	9	100	16	10	102	14	10	0.71	0.82
Dabigatran	48	35	-	13	40	1	7	42	-	6	38	1	9	40	1	7	0.51	0.57
Dosing level (3)																		
Perindopril	620	296	240	84	376	185	59	411	157	52	331	218	71	374	179	67	0.69	0.73

Fenofibrate	150	96	33	21	85	43	22	101	31	18	78	49	23	96	33	21	0.74	0.77
Metformin	956	377	133	446	232	173	551	402	113	441	335	198	423	371	128	457	0.58	0.68
Pregabalin	68	31	4	33	36	2	30	45	1	22	33	3	32	41	1	26	0.21	0.64
Dosing Level (4)																		
Gabapentin	63	18	7	38	15	4	44	26	2	35	14	2	47	22	5	36	0.54	0.57

Table 6.3 Concordance in renal drug dosing among the renal function estimating equations

Abbreviation: A- appropriate dose, IA- inappropriate dose that is defined as inappropriately high dose and contraindicated prescriptions, NR- dose modification not required

*not normalised to body surface area

#Dosing level refers to the number of kidney function categories for dose adjustment as specified in AMH.

The last column shows the Fleiss Kappa value which indicates the level of concordance among the three equations CG, MDRD, CKD-EPI (both normalised for BSA and non-normalised for BSA) in dosing of the renally-cleared drugs.

Drug	Kappa value Average Pairwise Percent Agreement (%)	
	MDRD* (mL/min)	CKD-EPI* (mL/min)
Alendronate	0.46 90.1	0.60 92.0
Risedronate	0.52 95.0	0.61 95.5
Sitagliptin	0.73 90.4	0.81 92.8
Dabigatran	0.50 83.3	0.55 85.4
Perindopril	0.63 79.1	0.71 83.8
Fenofibrate	0.69 84.6	0.90 95.3
Metformin	0.57 73.9	0.70 84.6
Pregabalin	0.55 75.0	0.85 92.6
Gabapentin	0.63 79.6	0.70 85.9

Table 6.4 Concordance in dosing recommendations using the Cockcroft-Gault versus MDRD and CKD-EPI equations

Abbreviation: MDRD, Modification of Diet in Renal Disease Study equation; CKD-EPI Chronic Kidney Disease – Epidemiology Collaboration

*not normalised to body surface area

S.N.	Patient characteristics				Estimated renal function			Prescribed dose		Recommended dose based on renal function		
	Gender	Age (yrs)	Weight (kg)	SrCr (μmol/L)	CG	MDRD	CKD-EPI	Description	Dose/day (mg)	CG	MDRD	CKD-EPI
1	F	83	104	100	61.7	48.8	45.1	Clodronate 800mg Tab, 2 nocte	1600	A	IA	IA
3	M	86	59	123	31.9	51.4	45.6	Dabigatran 110mg Cap, 1 bd	220	IA	NR	IA
4	F	80	65	140	29.0	33.4	30.6	Duloxetine 60mg Cap, 1 m	60	IA	NR	NR
5	F	85	58	71	46.7	72.1	67.2	Fenofibrate 145mg Tab, 1 midday	145	IA	NR	NR
6	F	83	76	150	30.0	30.6	27.6	Gabapentin 300mg Cap, 1 tds	900	A	A	IA
7	M	85	70.2	120	39.6	53.1	47.3	Glibenclamide 5mg Tab, 2 bd	20	CI	NR	CI
8	F	81	64	65	60.4	80.7	76.9	Levetiracetam 1000g Tab, 1 bd	2000	A	NR	IA
9	M	82	58.8	144	29.1	43.3	38.7	Memantine 20mg Tab, 1m	20	IA	NR	NR
10	F	93	51.6	110	22.9	42.7	37.4	Metformin 850mg Tab, 1bd	1700	CI	NR	IA
11	F	78	69	85	52.3	59.6	56.8	Pregabalin 150 mg Cap, 1 d	150	IA	A	IA
12	F	87	50.5	126	22.1	37.0	33.1	Risedronate 35mg Tab, 1 weekly	5	CI	NR	NR
13	M	58	88	125	71.0	54.7	54.4	Saxagliptin 5mg Tab, 1d	5	A	NR	NR

14	M	78	75	127	45.0	50.6	46.4	Sitagliptin 100mg Tab, 1 mane	100	IA	NR	IA
15	M	69	96.6	205	41.2	29.8	27.7	Solifenacin 5mg Tab, 1 d	5	NR	NR	A
16	F	80	105	144	46.0	60.6	58.0	Strontium 2000 mg, 1 nocte	2000	NR	NR	CI
17	F	78	87	104	53.9	47.3	44.5	Vildagliptin 50mg Tab, 1 bd	100	NR	IA	IA
18	M	92	65	150	25.6	40.4	34.4	Zoledronic acid 5 mg, mdu	5	IA	NR	IA

Table 6.5 Examples of discrepancies among the equations

A-appropriate dose, NR-dose adjustment not required based on renal function, CI-contraindicated, SrCr-serum creatinine

6.5 Discussion

We found a statistically significant difference in the kidney function estimations rendered from the three equations in the same group of patients. The overall differences in the mean eGFR values were quite small; however, at an individual level they gave estimates that differed substantially. We cannot determine which equation best approximated the true kidney function in our study due to lack of actual measures of kidney function. Further, the validation of the equations was not the purpose of this study.

We found a good agreement between the eGFR and eCrCl for dosing of non-critical drugs. Our results suggest that the equations have moderate-substantial agreement in dosing of non-critical drugs in primary care settings. This finding is consistent with the study by Steven *et al*, which concluded that there was little difference in the drug dose that would be administered using eCrCl and eGFR.²⁴³ The normalisation of eGFR had an impact on drug dosing decisions; there was a higher level of agreement among the equations when the normalisation to BSA was removed from the eGFR values. This aligns with the United States National Kidney Disease Education Program's (NKDEP) suggested approach that either an eCrCl or an eGFR with BSA normalisation removed, are acceptable for drug dosing estimations.²⁴⁴

We found that the CKD-EPI equation, not adjusted for BSA, had the highest concordance with the Cockcroft-Gault equation for both estimating renal function and the dosing of the renally-cleared drugs. This finding is consistent with the previous literature which demonstrated that the CKD-EPI equation non-normalised to the BSA correlated more closely with the Cockcroft-Gault equation than did other formulae.²⁰³ Similarly, in another study, the non-normalised CKD-EPI equation (mL/min) was found superior to the normalised CKD-EPI equation in estimating GFR (mL/min/1.73 m²) for drug dosing.²⁴⁵ Using the GFR (mL/min) as the reference for dosing, the CKD-EPI with the removal of BSA normalisation (mL/min) was associated with greater dosing concordance of carboplatin.²⁴⁵

The non-normalised CKD-EPI (mL/min) provided results, which were less biased and comparable at predicting GFR (mL/min) at higher levels of GFR and body mass index.^{246 247} A possible explanation for these findings would be that in this and the previously mentioned studies, the mean BSA for the sample was about 2 meter square.²⁴⁷ The BSA of 1.73 m² is the average normal mean value for young adults. The main purpose of reporting eGFR normalised to BSA was to allow harmonisation of results in individuals of various body size.²⁴⁸ The

normalisation or removal of this will have little effect for patients whose BSA is close to 1.73 m². However, for elderly people, or in patients whose body size is very different than average, the BSA should be considered.

The Cockcroft-Gault equation has been used as the preferred method to assess kidney function for drug dosing in the past. With the introduction of new classification of CKD, the new MDRD equation was used for diagnosing and staging CKD. This equation was later suggested for drug dosing. However, more recently, it has been suggested that the CKD-EPI is the most accurate method for estimating GFR.^{102 157} Compared with the MDRD study equation, it provides less negative bias at values higher than 60 mL/min/1.73m² and more accurate estimation of eGFR in diverse populations.¹⁰² Use of a single kidney function estimate for detection, drug dosing and management of CKD would facilitate better health care delivery in the primary care setting.²⁴⁹ With laboratories automatically reporting CKD-EPI eGFR estimates, this equation, if validated for drug dosing, would be a useful tool for health professionals and potentially address the confusion associated with the existing practice of using different formulae for different purposes.

The performance of renal estimating equations in renal dosing has been evaluated in various instances and discrepancies have been reported. However, very little is known regarding the clinical outcomes of the observed discrepancies.²⁵⁰ The differences in dosing based on different estimates of creatinine clearance may, in many cases, be clinically unimportant, or can be further refined based on clinical response. There is a need for a long-term multi-centre study in diverse populations to define the clinical effects of such discrepancies. In the interim, for individuals in whom the three equations provide substantially different estimates of kidney function or when prescribing drugs with narrow therapeutic indices or dose-dependent toxicities, assessing kidney function using alternative methods such as measured CrCl or measured GFR using exogenous filtration markers, should be considered. It is also recommended that prescribers use the available estimates along with their best judgement and clinical response to determine renal dosing for individual patients.^{251 252}

It should be noted that most of the discrepancies in drug dosing between equations might occur near the boundary between levels of renal function. These cut-offs could be arbitrary and not very precise with regards to drug clearance. In some cases, doses can double depending on which side of the boundary the renal function estimation falls. Moreover, it is accepted that clinical decisions may often over-ride the renal dose recommendations.

Laboratories provide serum creatinine measurements based on the creatinine assays that are aligned to the reference isotope-dilution mass spectrometry (IDMS) in Australia.¹⁰³ The MDRD Study equation has been re-expressed for standardised serum creatinine.¹⁰¹ The CKD-EPI equation was developed using creatinine assays that are IDMS-aligned. However, the Cockcroft-Gault equation has not been re-expressed for use with standardised serum creatinine.²⁵³ This might have contributed to the observed discrepancies among the equations.

The MDRD equation has been found to have a negative bias at values higher than 60 mL/min/1.73m².²⁵⁴ This equation tends to overestimate eGFR values in patients above 60 mL/min/1.73 m², indicating need for dose adjustment less frequently.²⁵⁵ Some of the drugs examined in the study, such as metformin, gabapentin and pregabalin, have dose adjustments recommended near or above 60 mL/min. We did not evaluate the various corrections or modifications of the Cockcroft-Gault equation that have been proposed, such as using lean or ideal body weight. We only did the analysis for CrCl estimated based on actual body weight.

6.6 Conclusions

There is need for a long-term multi-centre study in a diverse population to define the clinical effects of the discrepancies among the equations for drug dosing. Given the greater concordance of the non-normalised CKD-EPI equation with the Cockcroft-Gault equation for dosing, the recommendation by Kidney Health Australia and the United States National Kidney Disease Education Program that ‘dosing based on either eCrCl or an eGFR with body surface area normalisation removed are acceptable’, seems suitable and practicable for the purpose of dosing of non-critical drugs in the primary care setting.

6.7 Next step

The aforementioned studies examined the factors contributing to the problem of dosing error in patients with CKD. These included a lack of quantitative data in the available drug information sources, and contradiction and inconsistency in dosing information among the PI, in addition to confusion surrounding the use of renal function estimating equations for drug dosing purposes.

In the next chapter, we present the findings of a survey we undertook to understand the factors associated with inappropriate prescribing of medications in patients with CKD from the

prescriber's perspective. We also aim to understand the GPs' views on applicability, utility and the potential barriers to using the available guidelines and information sources for drug dosing purposes in primary care settings. Ultimately, we will identify the areas that need intervention to improve dosing in patients with CKD. This will assist in the design of interventional programs aimed at improving the quality of care in patients with CKD.

Chapter 7 POTENTIAL BARRIERS TO THE USE OF AVAILABLE GUIDELINES AND INFORMATION SOURCES FOR RENAL DRUG DOSING PURPOSES: A SURVEY OF GENERAL PRACTITIONERS

7.1 Abstract

Introduction. General Practitioners (GPs) are the frontline caregivers for patients with chronic kidney disease (CKD) and are provided with access to evidence-based guidelines to support them in optimal medication management. Nonetheless, studies have documented suboptimal prescribing in patients with CKD in Australian primary care settings. This study examines the potential barriers to optimal management of medications in CKD from the prescriber's perspective.

Method. A web-based survey of Australian GPs was conducted. The survey was divided into three sections, covering demographic and professional practising information, approach to drug dosing in CKD, and barriers to using the current guidelines and how these could be overcome.

Results. One hundred and fifty-eight GPs completed the survey. The majority of the GPs were males (64.6%) and the median duration of clinical practice was 20 years. In general, there was low familiarity with CKD management guidelines and a lack of confidence in identifying and dosing renally-cleared drugs. Limited time or more urgent patient issues and fear of being perceived as 'over-servicing' for pathology testing, were prominent factors felt to limit ordering a kidney function test. GPs have embraced electronic resources to a greater extent than paper-based information sources. The MIMS was the most widely used information source. There was a general scepticism expressed concerning the usefulness, reliability and applicability of the information sources for renal dosing. The major barriers to using guidelines were lack of easy access during consultations and inadequate or ambiguous recommendations on renal dosing. The factors responsible for inappropriate prescribing from the GPs' perspective were a lack of awareness on the availability of information sources and lack of routine renal function testing. Clinical decision support systems and online training and education were the most preferred interventions, as ranked by the GPs.

Conclusion. Updating the information sources to present the key elements in an unambiguous format, in conjunction with efforts to build consensus among the standard information sources, seems necessary. As a result of this, GPs can incorporate the recommendations into practice. Improved dissemination of existing guidelines, online education to increase awareness on drug

dosing, available guidelines and how to use them, and decision support system to aid GPs in identifying renally-cleared drugs, also appear warranted.

7.2 Introduction

Chronic kidney disease (CKD) is a major health problem in Australia, and globally, due to its increasing prevalence and close association with morbidity and mortality.²⁵⁶ It has been estimated that 10% of all adults presenting to a general practice in Australia have CKD and 80% have at least one risk factor for CKD.³⁸ Every day, more than five Australians commence dialysis or transplantation.²⁵⁷ Data from Kidney Health Australia indicates that the number of patients with end-stage kidney disease (ESKD) tripled between 1991 and 2009, and is projected to continue to rise during the next decade; increasing by nearly 80% between 2009 and 2020.²⁵⁸

Early diagnosis, timely referral to nephrologists and optimal medication management, play significant roles in delaying the progression of CKD or preventing the occurrence of ESKD.²⁵⁹ However, due to the asymptomatic nature of the disease, kidney damage typically goes unnoticed until the stage where the therapeutic interventions are often ineffective.⁷⁰ Therefore, CKD must be actively sought to be recognised and managed. CKD screening is recommended by several nephrology professional bodies, with the intent of limiting or preventing CKD progression, inappropriate drug dosing and nephrotoxic injury.²⁶⁰

Impaired renal function has pronounced effects on the pharmacokinetic and pharmacodynamics properties of many drugs; therefore, optimal drug selection and dose modification are imperative to optimise patient outcomes and minimise drug-related problems.^{82 186} It is important to review renally excreted medications and avoid nephrotoxic medications in people with CKD.¹⁰⁹ Dosage reduction or cessation of renally excreted medications is generally required once the GFR falls below 60 mL/min/1.73 m².³⁸²

General practices are the best place to screen for and manage CKD, with 80% of Australians visiting their local General Practitioners (GPs) for care at least once a year.²⁶¹ GPs are the frontline caregivers for patients with CKD. Typically, CKD identification is best performed in primary care and can be managed without referral to a specialist. GPs are the primary decision-makers when it comes to prescribing medications, and are provided with

² About half of the drugs included in our drug list (appendix 1) required dosage adjustment based on renal function only at CrCl≤30 mL/min

various electronic tools with access to evidence-based guidelines and standard drug information sources to support them in optimal medication management in CKD. However, analysis of prescription records from tertiary care hospitals and aged care facilities within Australia suggests a high proportion of suboptimal prescribing for patients with CKD.^{128 140} These findings are consistent with results from overseas studies, which indicate low adherence to renal dosing guidelines, leading to inappropriate prescribing for patients with CKD in community settings.⁹⁻¹⁵ While the problem of suboptimal prescribing for community-based patients with CKD has been well identified and studied in Australia, the reasons have not been researched. A proper understanding of this is needed to design interventions aimed at improving the quality of prescribing for patients with CKD.

Studies conducted in the USA have shown that renal dosing guidelines are often overlooked and this is a major contributor to overall inappropriate prescribing and drug-related problems in aged care facilities.^{9 12} GPs have expressed difficulty in deciding whether there is a need for renal function assessment and have acknowledged the complexity of medication regimens in patients with CKD.^{20 21 262} GPs were reluctant to diagnose CKD on the basis of a glomerular filtration rate, and felt that labelling older people as having CKD was problematising aging.²⁰ Some studies indicated difficulty faced by GPs in explaining the disease to patients, where they feared alarming people by diagnosing them, especially in early-stage CKD.^{20 262}

While the literature is replete with reports on GPs' awareness about CKD management guidelines and nephrologist referral practices among primary care physicians,^{17 21 263} there is limited information available on the potential barriers to optimal management of medications in CKD from the prescriber's perspective. Little is known about information sources that GPs use when deciding on drug doses for patients with CKD. To date there has not been any studies conducted to identify GPs' perspectives regarding the applicability and utility of these guidelines in patients with CKD.

We were interested in undertaking a survey to understand the options available to GPs to assist in managing medications in patients with CKD and to assess GPs' views on applicability, utility and potential barriers in using the available guidelines and information sources for drug dosing purposes in primary care settings.

We were interested to find out whether the GPs know about currently published CKD guidelines, whether they have used them, and whether they considered their practice had

changed since the provision of laboratory-provided eGFR. We also wanted to know how GPs would respond to a set of statements generated from debates in the current literature regarding the use of particular drugs in CKD. We wanted to know the level of confidence they have in dosing of renally-cleared drugs. Finally, we were interested to determine what sort of strategies to improve medication use in renal disease were most likely to have acceptance and use by GPs.

7.3 Methods

7.3.1 Ethics approval

Ethical approval for the study protocol was granted by the Tasmanian Health and Medical Human Research Ethics Committee Tasmania, Australia (H0015068).

7.3.2 Design, Participants and setting

A web-based, cross-sectional survey of Australian GPs was conducted for 12 weeks between 1st December 2015 to 1st March 2016. The survey were designed using LimeSurvey open source PHP web application software (<http://www.limesurvey.org>) and was hosted online at the University of Tasmania. A sample of 4000 GPs identified from the National Health Services Directory were sent an invitation via email to take part in the online survey.²⁶⁴

7.3.3 Questionnaire design and content

Questionnaire items and the theoretical basis for the questionnaires were identified from the literature review.^{17 18 20 21 24 265} The survey was divided into three sections covering: demographic and professional practising information, approach to drug dosing in CKD, preferred drug information source for renal drug dosing and barriers to using them, and how they can be overcome (Appendix 2). The questions were a mixture of multiple choice, open ended, rank-order and Likert-type questions.

Questions were designed to assess how frequently GPs encountered problems with deciding dosages for patients with CKD and, to identify the factors that prompt the GPs to perform renal function measurement or drug dosing. The participants were asked about the guidelines or information sources they use for drugs dosing purposes and if they observe any obstacles in using them. GPs could select multiple barriers, including information sources,

patient factors, lack of time etc. Because studies indicate that drugs like bisphosphonates, ACE-inhibitors and metformin are more likely to be prescribed inappropriately in patients with CKD, and given the added ambiguous, conflicting information about their use in literature, we focused some questionnaire items on recognising GPs' opinions on using these drugs in patients with CKD. A four-point Likert scale was used to rate the feasibility, reliability and utility of the guidelines. The survey questionnaires also explored whether the GPs recognise the need for intervention to optimise drug dosing for patients with CKD.

A draft questionnaire was prepared and pre-tested among the investigators and minor changes in word selection and instructions were made to the questionnaire.

7.3.4 Survey implementation

A personally addressed email that included a brief description of the study, the investigators' affiliation, and a link to the survey were sent to the GPs. A click on the link redirected them to the survey page. Emails contained statements ensuring confidentiality, and the respondents were offered an opportunity to anonymously participate in a draw for a prize (e.g. Apple iPad) to encourage participation (Appendix 3, sample of invitation email).

7.3.5 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. and Excel 2010 (Microsoft Corporation, Redmond, USA). Data were summarised using descriptive statistics, including means (\pm standard deviation) for continuous variables and proportions/percentages for categorical variables. Pearson Chi-squared and Kruskal-Wallis test were used to determine the association between variables. Spearman's rank correlation coefficients were calculated for measuring correlations. For the open-ended questionnaires, comments were entered in a word processing program and organised by question number. Investigators determined the themes and categorised the comments.

7.4 Results

Of the random 4000 email addresses identified from the National Health Services Directory, 45% of the addresses were non-operational and 10% responded with automatically

generated emails indicating the GPs were out of the office. A total of 189 GPs clicked on the survey link and were directed to our survey page. Of these, 158 filled out the survey, equating to a response rate of 7.2%. This included 125 respondents who completed all the questionnaires and 33 respondents who partially completed the survey, answering between 25 to 29 questions each (Figure 7.1).

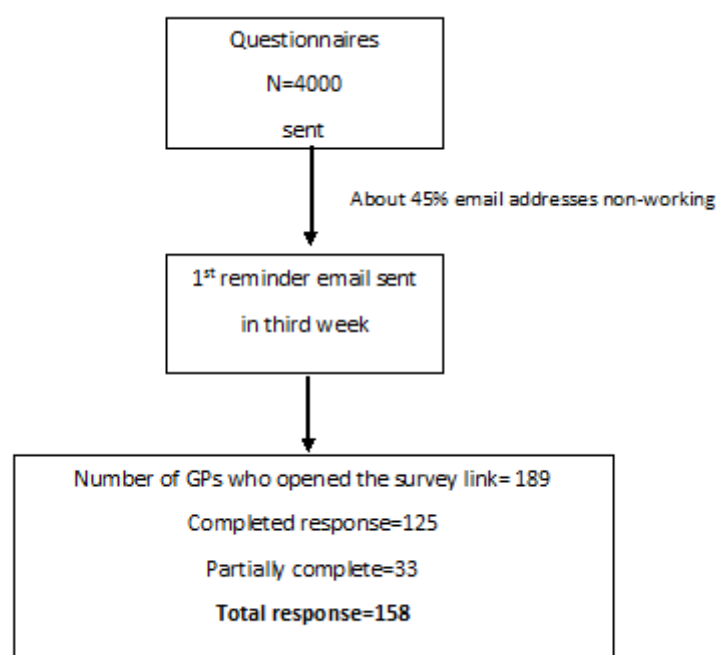


Figure 7.1 Survey implementation and responses

7.4.1.1 Participant Characteristics

GPs practising in New South Wales (45, 28.5%), Victoria (39, 24.7%), South Australia (27, 17.1%), Queensland (14, 8.9%), Tasmania (23, 14.6%), Western Australia (9, 5.7%) and the Northern Territory (1, 0.6%), filled out the survey. Respondents' characteristics are summarised in Table 8.1 The majority of respondents were male (64.6%) and the median for clinical practice was 20 years, with a range of one to fifty-five years. The median number of CKD patients seen by the GPs per week was 6, with a range of 1 to 90 patients. There was a fairly even distribution of GPs across practice locations. The GPs generally used electronic prescribing software in their practice (97.5%). Medical Director and Best Practice were the most widely used prescribing softwares (Table 7.2).

Variables	N (%)	Mean (SD)
Gender		
<i>Female</i>	56 (35.4)	
<i>Male</i>	102 (64.6)	
Years in profession		20 (15)
≤ 5	35 (22.2)	
5-10	23 (14.6)	
10-25	37 (23.4)	
25-30	17 (10.8)	
30-35	25 (15.8)	
>35	21 (13.3)	
State		
New South Wales	45 (28.5)	
Victoria	39 (24.7)	
South Australia	27 (17.1)	
Queensland	14 (8.9)	
Tasmania	23 (14.6)	
Western Australia	9 (5.7)	
Northern Territory	1 (0.6)	
Practice location		
<i>Urban</i>	56 (35.4)	
<i>Suburban</i>	55 (34.8)	
<i>Rural</i>	46 (29.1)	
<i>other</i>	1 (0.6)	
No. of patients with CKD seen per week		9.6 (11.8)
Mode of prescribing		
<i>Electronic prescription</i>	154 (97.5)	
<i>Paper-based prescription</i>	4 (2.5)	

Table 7.1 Respondent characteristics

Continuous variables are presented as means with standard deviations. Categorical variables are expressed as percentages and N.

Software	Frequency	Percent
None*	4	2.5
Medical Director	64	40.5
Best Practice	68	43
ZedMed	5	3.2
Genie	7	4.4
MedTech32	2	1.3
Practix and Profile	2	1.3
Others	6	3.8
<i>Monet</i>	<i>1</i>	
<i>Communicare</i>	<i>3</i>	
<i>Medinet</i>	<i>2</i>	
Total	158	100.0

Table 7.2 Common prescribing software among the GPs

*used paper-based prescription

7.4.1.2 Preferred renal function measure for drug dosing

More than half of the participants reported that they use laboratory eGFR for the purpose of drug dosing. 20.8% (n=33) claimed that they use serum creatinine for drug dosing and 18.3% (n=29) reported that they use CrCl for drug dosing (Figure 7.2). There was no significant association between preferred renal function measure of choice and GPs' demographics (gender, location, setting, years of practice and number of patients with CKD seen in a week).

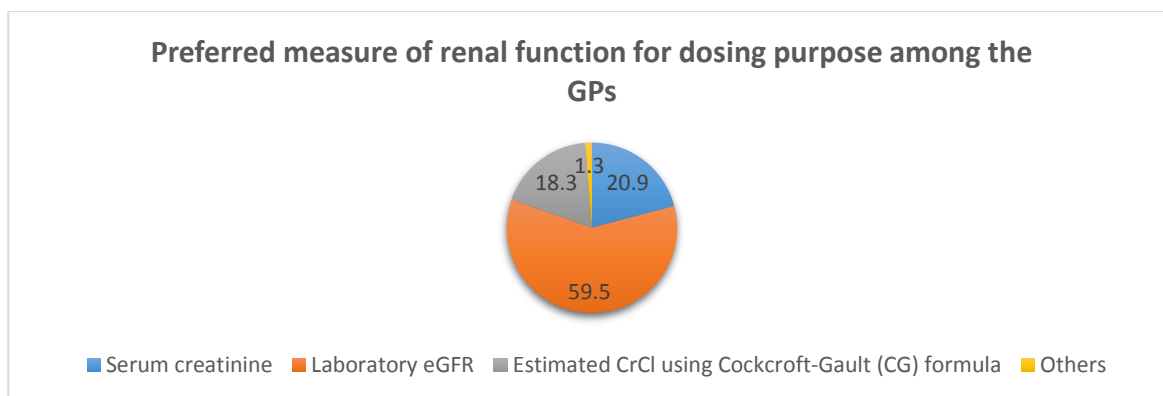


Figure 7.2 Renal function measure of choice

(N=158)

For the prescription of drugs in elderly patients, 60.1% (n=95) claimed to take the laboratory provided eGFR into account, 24.7% (n=39) considered serum creatinine, 13.3% (n=21) took account of estimated creatinine clearance and 1.9% (n=3) of GPs were unsure about which renal function measure should be considered. (Figure 7.3)

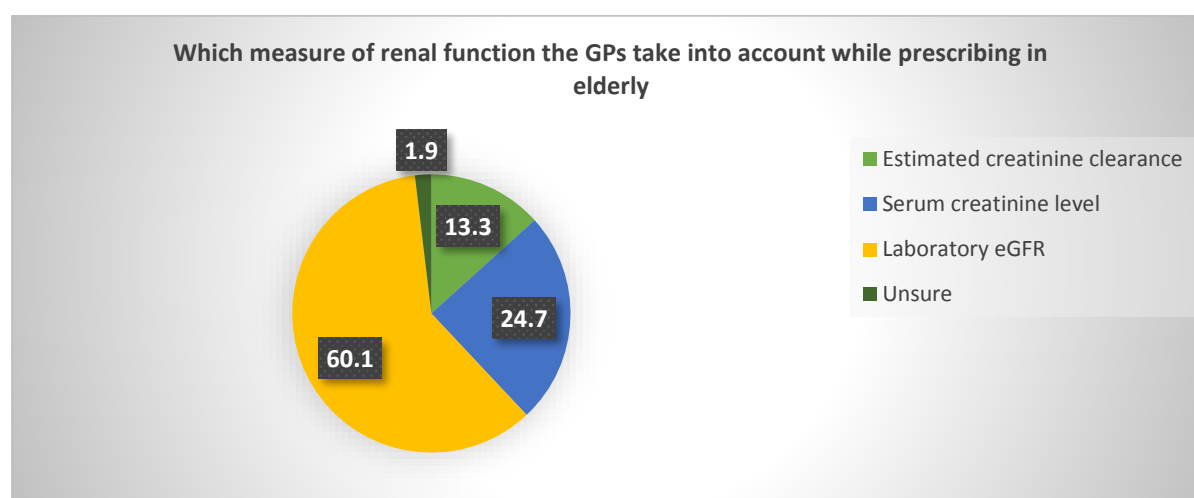


Figure 7.3 Renal function measure taken into account in elderly

N=158

Before prescribing medication to an elderly patient, 46.8% (n=74) of the GPs evaluated renal function only for certain drugs, 36.1% (n=57) evaluated regularly, even for a repeat prescription, and 24.1% (n=38) evaluated for all the new drugs. (Figure 7.4)

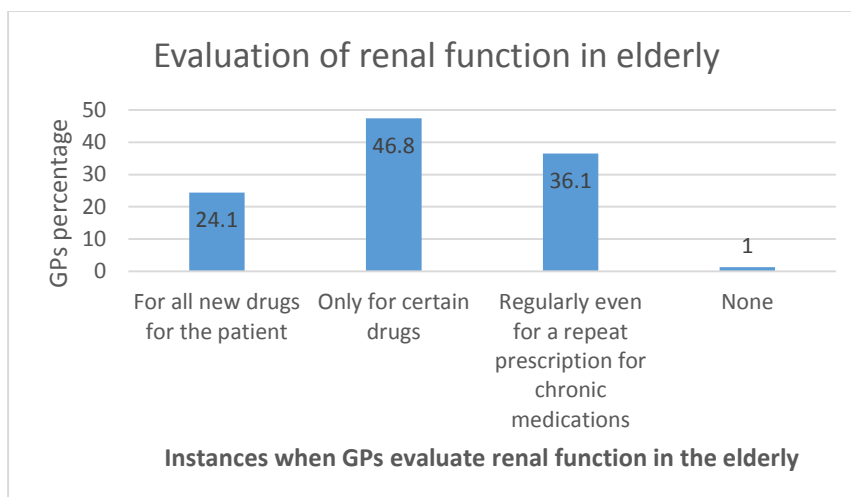


Figure 7.4 Evaluation of renal function in elderly

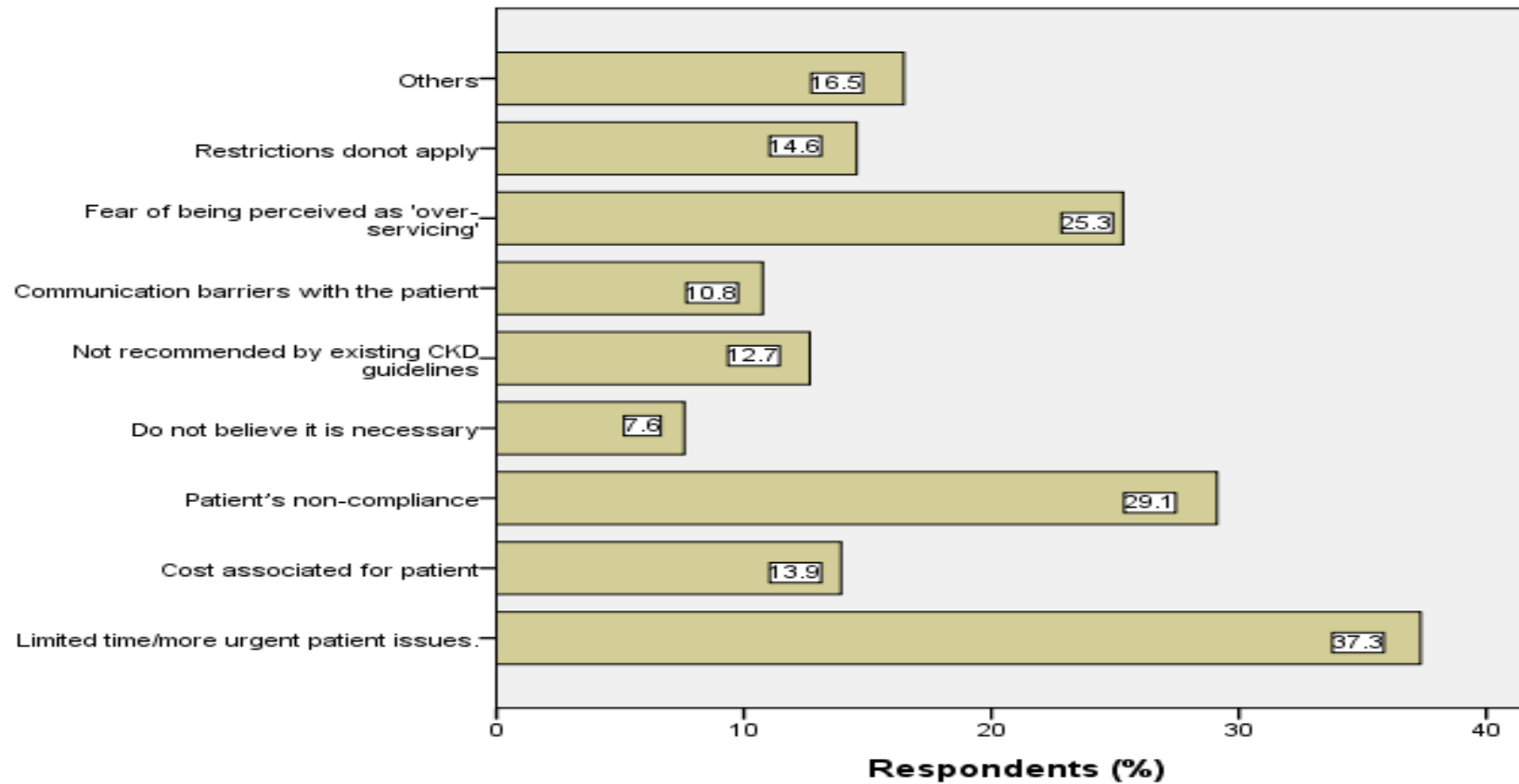
Percentages do not sum to 100 as multiple responses were possible. N=158

7.4.1.3 Barriers to ordering a renal function tests

The majority of the GPs (56.9%, n=90), reported that it is fairly practical or feasible to assess renal function before prescribing renally-cleared drugs; 29.7% (n=47) reported that it is very practical or feasible, 10.1% (n=16) GPs reported that it is not practical or feasible and 3.2% (n=5) of the GPs were unsure.

GPs were asked if they recognise any of the seven given factors as obstacles to ordering a renal function test. Limited time or more urgent patient issues, patient's non-adherence and fear of being perceived as 'over-servicing' were the top three factors believed to generally limit ordering a kidney function test (Figure 7.5). The questionnaire also had an open-ended option to capture other obstacles not listed.

Barriers to ordering kidney function test as endorsed by the GPs



Percentages donot sum to 100 as multiple responses were possible. N=158

1

Figure 7.5 Obstacles to ordering a kidney function test

Other obstacles listed by the GPs were; confusion surrounding the current best accepted measure of renal function test, lack of access to pathology, timeframe of results, practitioner's inertia, logistics of getting some people to get a test before they need a drug, patient's preference to avoid blood tests, lack of patient's understanding about the importance of renal function, difficulty for patients and the cost to the community (Table 7.3).

<u>Patient's factors</u>	<u>External factors</u>
-Difficulty for patients	-Lack of acceptable recent renal function tests
-Lack of understanding on the importance of renal function monitoring	-Pathology access and result timeframe
-Cost to community	
-Patient time constraints esp. if elderly; patient mobility	
-Patient's preference to avoid blood tests	
<u>Prescriber's factors</u>	<u>Do not feel any restriction apply</u>
-Logistics of getting some people to get test before they need drug	-Everyone gets it when ordering bloods tests yearly
-Practitioner inertia	-I don't recognise any restrictions/concerns/barriers
	-Most patients with chronic health issues will have regular blood test. Hence, I have no issues with getting the kidney function test."

Table 7.3 Verbatim responses on barriers to ordering a kidney function test

7.4.1.4 GPs' use of automated laboratory eGFR

GPs had an overall positive attitude towards the automated eGFR monitoring. When asked about whether their overall approach to CKD diagnosis had changed since automated eGFR reporting, almost half of the GP 47.5% (n=75) said it had. However, 32.3% (n=51) said it had not and a minority [20.3% (n=32)] of respondents were unsure. (Figure 7.6)

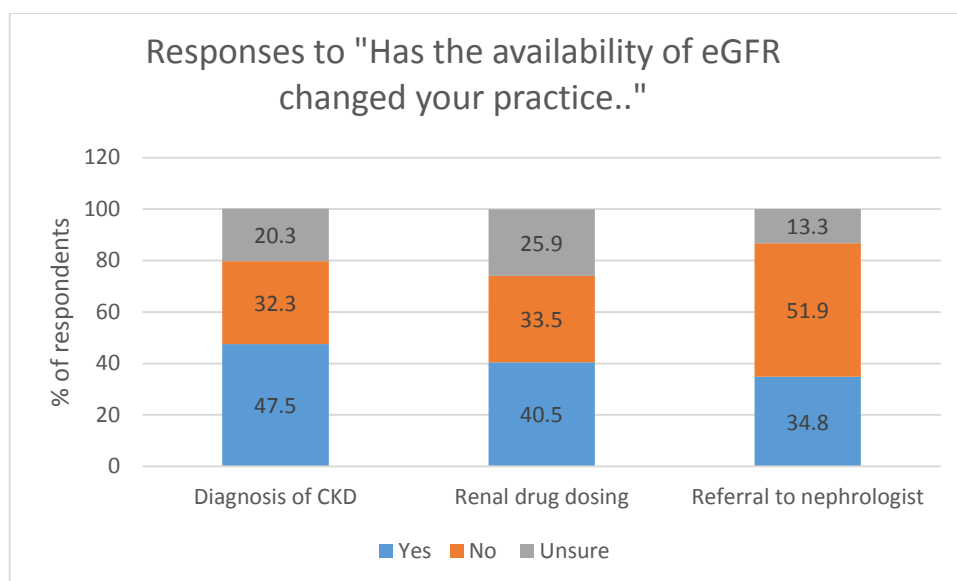


Figure 7.6 Responses to automated eGFR and change in practice

When asked if the laboratory eGFR has changed their overall approach to renal drug dosing, 40.5% (n=64) of the GPs believed it had changed their approach to drug dosing. However, 33.5% (n=53) believed it had not and 25.9% (n=41) respondents were unsure.

When asked if the eGFR had changed the practice of referral to nephrologists, 34.8% (n=55) of the GPs believed it had, 51.9% (n=82) believed it had not and 13.3% (n=21) respondents were unsure. The approach to referral to a nephrologist had not changed as much their approach to diagnosis and drug dosing.

Verbatim responses to how the automated eGFR has changed the way they diagnose CKD and perform drug dosing in CKD were organised into eight and ten themes, respectively (see Table 7.4 and Table 7.5). Based on the GPs' written feedback, the automated eGFR has increased awareness and enhanced detection of CKD making the diagnosis easier and efficient as indicated by the following quotes;

"It is a clearer way to pick up early CKD. I have a better stratification of risk based on using an eGFR."

"Previously if the creatinine was normal I did not really consider renal function when prescribing a lot of drugs in the elderly. The eGFR makes me stop to consider the drugs I am prescribing and any effect on renal function."

GPs indicated that consultation time was decreased; the eGFR streamlined their work and removed the need for calculating it themselves, and they often used it for dosage adjustment.

“Much easier than CrCl so I do it more often.”

“Do not use SrCr anymore.”

One GP expressed using eGFR as an additional tool to measure renal function that assists in renal dosing and used this for drug dosing selectively.

“For general purposes, in patients in the normal weight range, then I am happy to use the lab eGFR. However, for very thin or very overweight patients, on really dose critical drugs, then I would go looking for alternative measures to inform my dosing, but this always takes time, hence I don't do it for simple/straightforward drug dosing.”

Index of main themes

(A) Enhanced detection of CKD

Verbatim responses

- Easier to diagnose/identify (5)
- Easier to see reduced renal function, particularly trends
- I see it as easier to take note of
- It is a clearer way to pick up early CKD. I have a better stratification of risk based on using an eGFR

(B) Increased awareness

- Become aware of the whole issue, was scarily naive before
- I notice it more! It has raised more awareness of CKD (10)
- It helps to alert me to the possibility of CKD in a patient, which can lead me to investigate further.
- Made me more aware as adds weight to creatinine level
- More aware of renal impairment even when creatinine is almost normal in older patients
- I am more conscious of CKD with the eGFR in front of me
- More aware of deterioration & need to change treatment
- More aware because of easy availability
- More aware of renal impairment when prescribing medications
- More sensitive and aware
- More vigilant; also use urine ACR in conjunction with eGFR
- Think of it more often. I calculate CrCl using Cockcroft equation if I am worried about a particular patient or drug

(C) Enable CKD staging

- Easier to classify
- Give a percentage function of the kidney
- Gives a more easily compared unified number for serial monitoring across labs and longitudinally - can easily categorize as stage 3-5
- I can grade the CKD more easily and discuss risk factors more easily with the patient

(D) Increased prevalence/recognition of CKD

- Has allowed increased screening of patients for CKD
- CKD is more frequently diagnosed CKD
- Unrecognised CKD is not a problem anymore
- I do not overlook eGFR anymore
- More recognisable than creatinine; makes me take notice of deteriorating function

(E) Increased accuracy and simplicity in diagnosis of CKD

- It has generally simplified the process

	<ul style="list-style-type: none"> • It provides a reasonably accurate prompt to investigate patients at risk of CKD. • More information makes diagnosis simpler • Simpler monitoring for progression, change over time. • Simpler to sort out what is happening
(F) Increased confidence	<ul style="list-style-type: none"> • It has increased my confidence in deciding whether to prescribe a medication • Offered reassurance when eGFR is normal
(G) Improved productivity and time efficiency	<ul style="list-style-type: none"> • Able to calculate CKD quicker • Likely to just look at that, rather than to do a calculation • Prompts to work out creatinine clearance • Readily availability • It is now quicker and easier to diagnose
(H) Reliance on eGFR as primary measure of renal function	<ul style="list-style-type: none"> • Don't use Cockcroft-Gault formula any more • Don't really solely on serum creatinine • It's just easier than getting Creatinine clearance, so I use this test • No longer relying on the serum creatinine • Use eGFR a primary measure • Using eGFR rather than serum creatinine alone, as a guide • Calculated GFR is close to that from the lab so I now rely more on the lab result
(I) More concordance with the guidelines	<ul style="list-style-type: none"> • Guidelines use eGFR
(J) Better treatment decisions	<ul style="list-style-type: none"> • I can provide the correct dosing for the condition without affecting the kidneys • Offers a guideline to prescribing • Reduce or stop medications known to adversely affect eGFR
(K) An additional tool/information	<ul style="list-style-type: none"> • As reference review • I use it as a rough guide to creatinine clearance. • It adds a parameter that I can take into account along with creatinine and CrCl • I take it into account as a relatively "objective" measure

Table 7.4 Automated eGFR and changes in CKD diagnosis

Index of main themes	Verbatim responses
(A) More alert to need of dose adjustment	<ul style="list-style-type: none"> • More likely to flag it as an issue and review • Alert to changes 3 • Awareness of iatrogenic ARF • More frequently identified • More aware of reduced kidney function and its implications 2 • Extra red-flag to renal impairment • Extra market for highlighting renal function rather than creatinine alone • More aware • Makes me stop to consider the drugs I am prescribing and any effect on renal function • Reminds me to check and alter doses • Ready availability, increased awareness • Easier to diagnosis • More likely to take notice of dose changes required in renal failure. • Same as previous answer • Try to adjust drug dosage to stage of renal failure
(B) More likely to adjust dose	<ul style="list-style-type: none"> • I tend to adjust drugs more often • Makes me check PI to determine dose adjustments more often • Tend to change prescribing and reduce or delete medications which have an adverse effect on renal function, and more likely to adjust as a result of abnormal eGFR • I do dose adjustment more often as much easier than calculating CrCl
(C) Easier and quicker to adjust dose	<ul style="list-style-type: none"> • Easier to adjust • Easier and faster to estimate dose • It's quicker to calculate dose adjustment. • Simpler, clearer and quicker dose adjustments • Simpler to use
(D) Dose adjustment is more rigorous	<ul style="list-style-type: none"> • Spend more times with the patient • Useful and available measure • Using worsening eGFR to dictate treatment protocols
(E) Appropriateness of medication and dosing improved	<ul style="list-style-type: none"> • More careful dose adjustment • More informed • Dosage changes are based on eGFR

	<ul style="list-style-type: none"> • Certainly for anyone with eGFR less than 50 I double check items I am prescribing for them • Medications that are nephrotoxic, or medications that are cleared primarily through the kidneys, will be dose adjusted or be changed to alternative medications.
(F) More aligned to guidelines	<ul style="list-style-type: none"> • Doses are adjusted according to eGFR on prescribing guidelines • Drug dosing guidelines appear to refer more commonly to eGFR than creatinine levels. • I look up the PI when eGFR is below normal • It provides an accessible figure used by drug companies to tailor dose adjustment according to the measure. • I tend to rely on this as a gauge of the presence and severity of renal failure when considering medication that is renally excreted • I will decrease the dose if the clearance is less or not prescribe the drug if it is excreted by the kidney • Use eGFR and recommended dosage regimes
(G) Follow a clear and consistent guidance protocol for renal dosing	<ul style="list-style-type: none"> • For general purposes, in patients in the normal weight range, then I am happy to use the lab eGFR. However, for very thin or very overweight patients, on really dose critical drugs, then I would go looking for alternative measures to inform my dosing, but this always takes time, hence I don't do it for simple/straightforward drug dosing. • I look up renal dose for the medication in question and act accordingly. • When the latest renal function result is available, I do either formally or informally, review the patient's medication regimen, and consider the dosage to see if an adjustment is indicated. • I will ring a renal physician if I'm particularly worried or don't know. It's always something that sits in the background of so many of our patients. • When I do note abnormal eGFR - I tend to check up if any of the patient's current medications make the renal function worse.
(H) More confident	It has made me more sure of dosing - and dose titration
(I) Do not use CrCl and Srcr anymore	<ul style="list-style-type: none"> • Much easier than CrCl so I use it more often • Use eGFR and recommended dosage regimes • Do not use CrCl anymore • Do not rely on SrCr anymore

Table 7.5 Automated eGFR and associated changes in drug dosing

7.4.1.5 Preference for drug dosing-CrCl or eGFR

When asked if the GPs used Cockcroft-Gault equation for estimating CrCl for drug dosing purposes, 45 respondents said yes. Of these, 22 used actual body weight and 19 were unsure given they used online calculators. 105 respondents said they used laboratory eGFR for drug dosing purposes, exactly as provided by the laboratory (Table 7.6).

	Number of respondents
Creatinine Clearance	45
<i>Actual body weight</i>	22
<i>Ideal body weight</i>	1
<i>Adjusted body weight</i>	2
<i>Unsure as I use online calculators</i>	19
<i>Use ideal or actual body depending upon body habitus</i>	1
Laboratory eGFR	105
<i>eGFR exactly as provided by the laboratory</i>	80
<i>Use eGFR normalised for the patient's body surface area</i>	5
<i>Use normalised eGFR only for patients with extremes of body weight</i>	14
<i>Unsure</i>	3
<i>Others</i>	3
	N=150

Table 7.6 GPs' preference for drug dosing: creatinine clearance or eGFR

7.4.1.6 Usage of controversial drugs in CKD

Respondents were asked about their agreement or disagreement to the set of statements generated from debates in the current literature regarding the use of drugs with some controversies in CKD. A total of 142 GPs responded to this question.

When asked if Angiotensin-converting (ACE) inhibitors and angiotensin II receptors (ARBs) can be safely prescribed at all stages of CKD and whether they should not be deliberately avoided just because GFR is reduced, 7.7% (n=11) of GPs strongly disagreed, 39.4% (n=56) mildly disagreed, 14.7% (n=21) neither agreed nor disagreed, 33% (n=47) agreed and 4.9% (n=7) strongly agreed. When asked if bisphosphonates can be used in all

stages of CKD with correct dosage adjustment, 10.5% (n=15), 26% (n=37), 35.2% (n=50), 27.4% (n=39) and 0.7% (n=1) of the GPs strongly disagreed, mildly disagreed, neither agreed nor disagreed, agreed and strongly agreed, respectively (Figure 7.7).

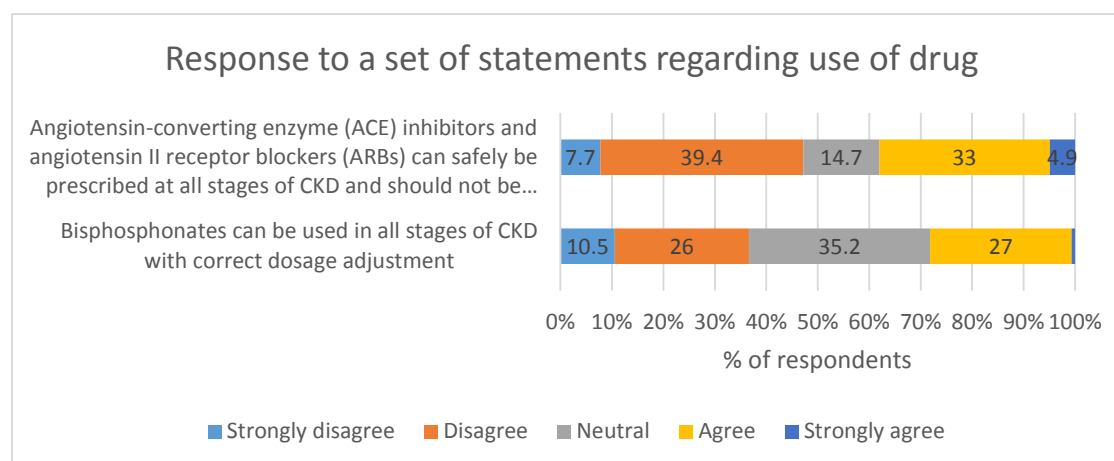


Figure 7.7 Usage of controversial drugs in CKD

N=142

7.4.1.7 Confidence in dosing of renally-cleared drugs

44.7% of GPs reported feeling confident in identifying and dosing of nephrotoxic drugs. 41.3% of GPs reported feeling confident in determining doses for ACE-inhibitors, 24.2% of the GPs were confident in determining the doses for bisphosphonates and 55.2% of the GPs were confident in determining the dose for metformin in patients with CKD (Figure 7.8).

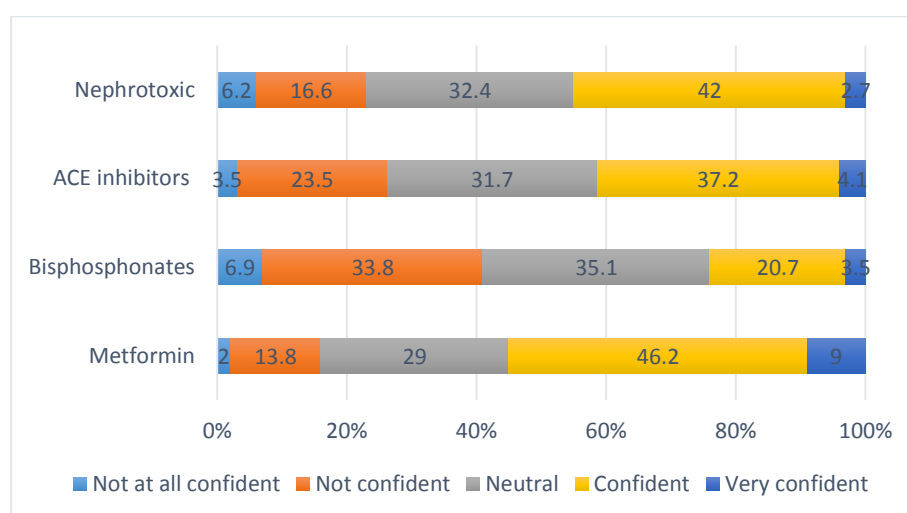


Figure 7.8 Confidence in renal drug dosing

N=145

A Spearman's rank-order correlation was run to determine the relationship between GPs' confidence and the demographic characteristics. There was a strong, positive correlation between GPs' confidence in identifying nephrotoxic drugs and length of professional practice, which was statistically significant ($P=0.04$). There was no correlation between gender or the number of patients with CKD (seen per week) with the confidence.

7.4.1.8 Information sources for renal drug dosing

The majority of the GPs 60.2% ($n=77$) experienced difficulties in deciding on drug dosage for patients with CKD (Figure 7.9).

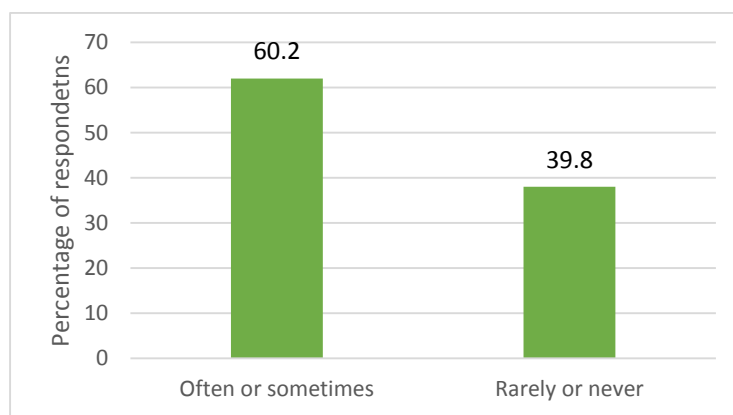


Figure 7.9 Difficulty in deciding drug dosage in patients with CKD

N=128

GPs were asked about their most preferred information source for deciding the dose in patients with CKD. A total of 128 GPs responded to this question. The MIMs, Therapeutic Guidelines and the AMH were the most widely used information sources among the GPs. Fifty percent of the GPs ($n= 64$) preferred MIMs/Product information, 19.5% ($n=25$) preferred Therapeutic Guidelines and, 11.7% ($n=15$) preferred the AMH, 3.9% ($n=5$) preferred the renal drug reference guide, 2.3% ($n=3$) preferred the British National Formulary (BNF), 3.1% ($n=4$) preferred contacting pharmacist and 9.4% ($n=12$) chose the option others. (Figure 7.10).

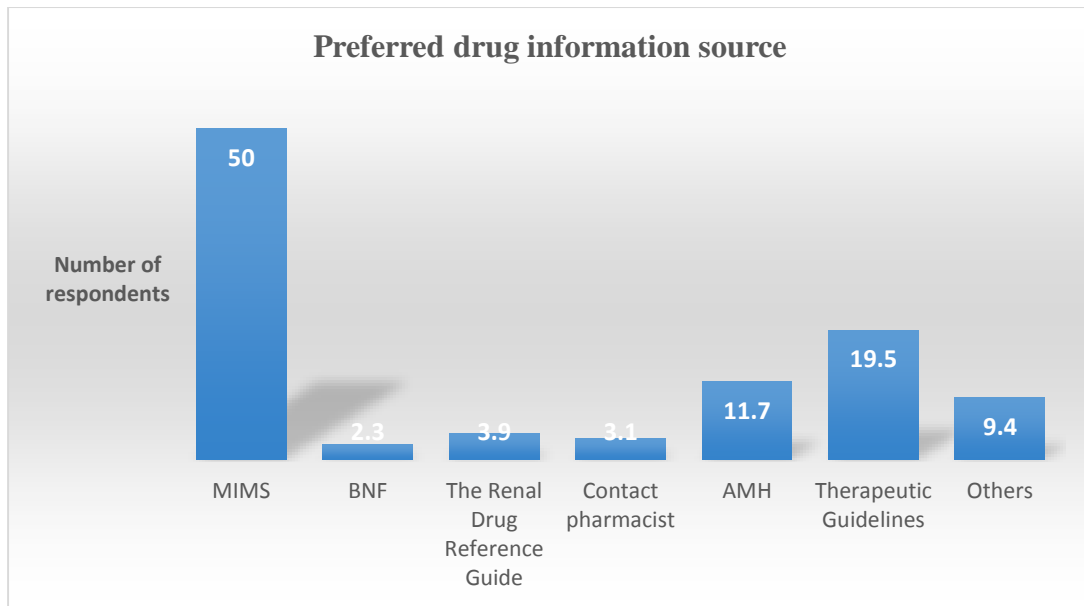


Figure 7.10 Preferred drug information sources

(N=128)

The majority of the GPs (81.6%, n=129 out of 158) responded that they access the drug information sources electronically and, 18.3% (n=29 out of 158) of the GPs reported that they access them as paper-based (print) drug information sources to extract information on renal dosing of the drug.

7.4.1.9 Guidelines' accessibility, reliability and applicability

Out of the 29 GPs who used paper-based information sources to gain information on renal dosing, 51.8% (n=15) responded that the information sources were easily accessible, 2.6% (n=6) said the guidelines were not easily accessible and 27.6% (n=8) were unsure. (Figure 7.11)

Out of the 129 GPs who accessed information sources electronically, 70.5% (n=91) responded that the guidelines were easily accessible; 24% (n=31) believed that they were not easily accessible and they take too much time navigating and 5.5% (n=7) of the GPs were unsure. (Figure 7.12)

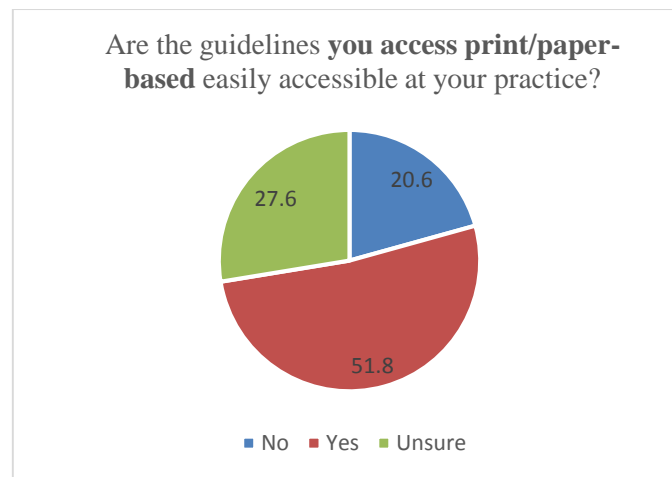


Figure 7.11 Accessibility of paper based guidelines

(N=29)

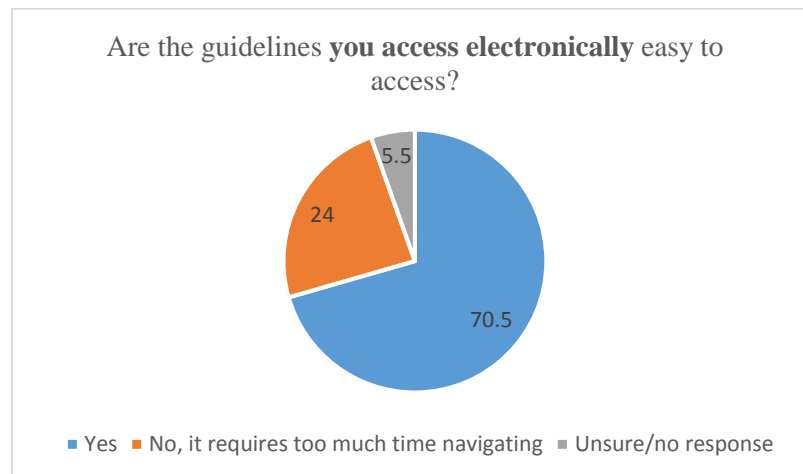


Figure 7.12 Accessibility of electronic guidelines

(N=129)

31.3% (n=40) GPs found CKD guidelines useful, 61.7% (n=79) found them to be fairly useful, 3.1% (n=4) found them to be unuseful and 3.9% (n=5) were unsure.

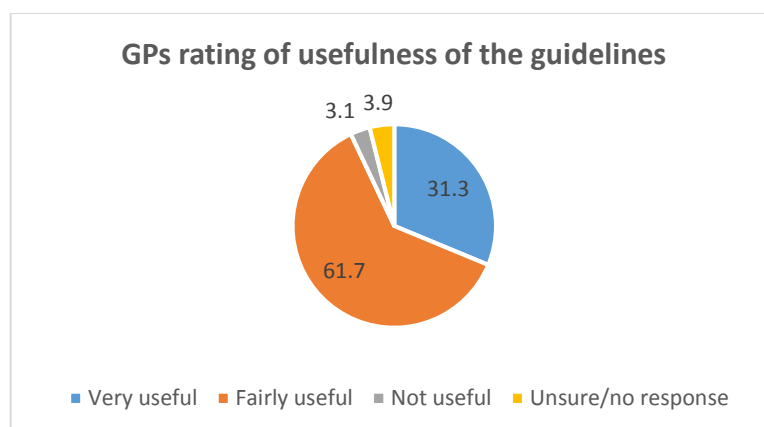


Figure 7.13 Usefulness of guidelines

(N=128)

69.5% (n=89) of the GPs found the guidelines to be very applicable, 10.2% of the GPs (n=13) found them to be not applicable and 20.3% (n=26) were unsure.

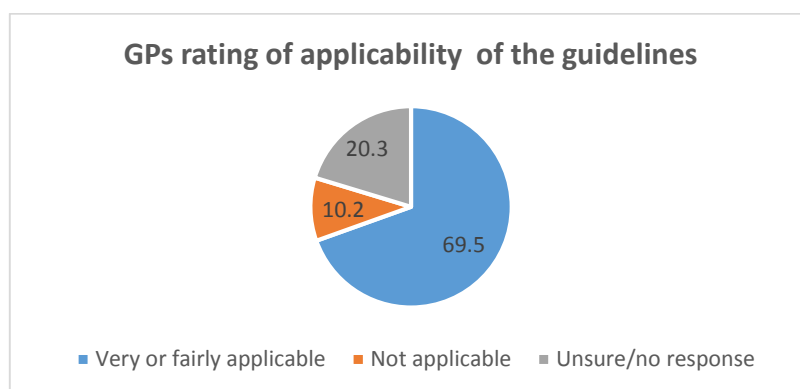


Figure 7.14 Applicability of guidelines

(N=128)

31.2% of the GPs (n=40) found CKD guidelines to be very reliable, 51.6% of the GPs (n=66) found them to be fairly reliable, 3.1% of the GPs (n=4) found them to be unreliable and 14% (n=18) were unsure.

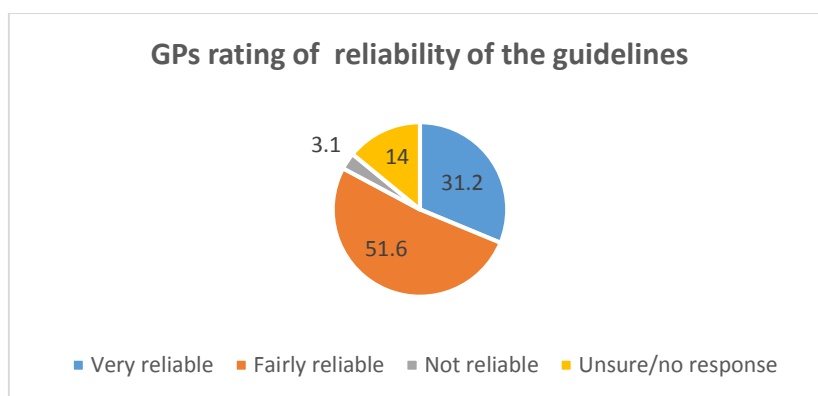


Figure 7.15 Reliability of guidelines

(N=128)

Familiarity with Kidney Health Australia guideline

41.8% (n=66) of the GPs believed that Kidney Health Australia's CKD management in general practice guidelines had been helpful in managing their patients with CKD. 35.5% (n=56) were not familiar with the guidelines and 13.2% (n=21) said they did not find the guidelines useful and 9.5% (n=15) were unsure (Figure 7.16).

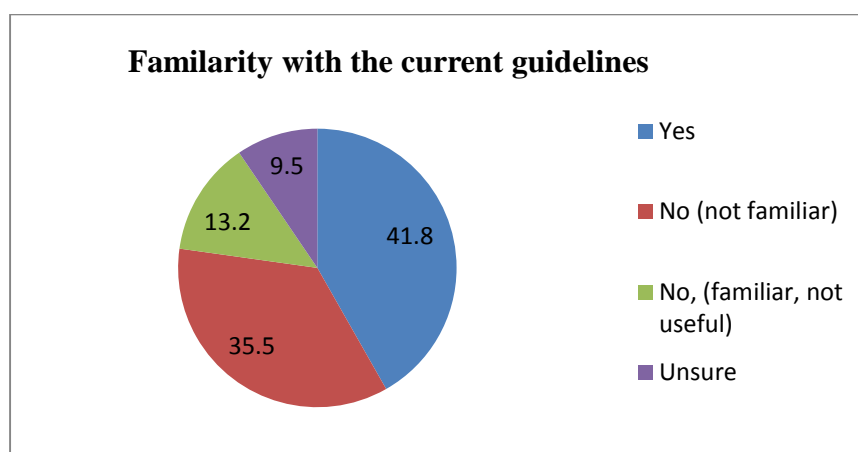


Figure 7.16 Familiarity with CKD guidelines

(N=158)

7.4.1.10 Factors limiting the access the guidelines

Commonly endorsed barriers to accessing the information sources to perform drug dosing are shown in Figure 7.17.

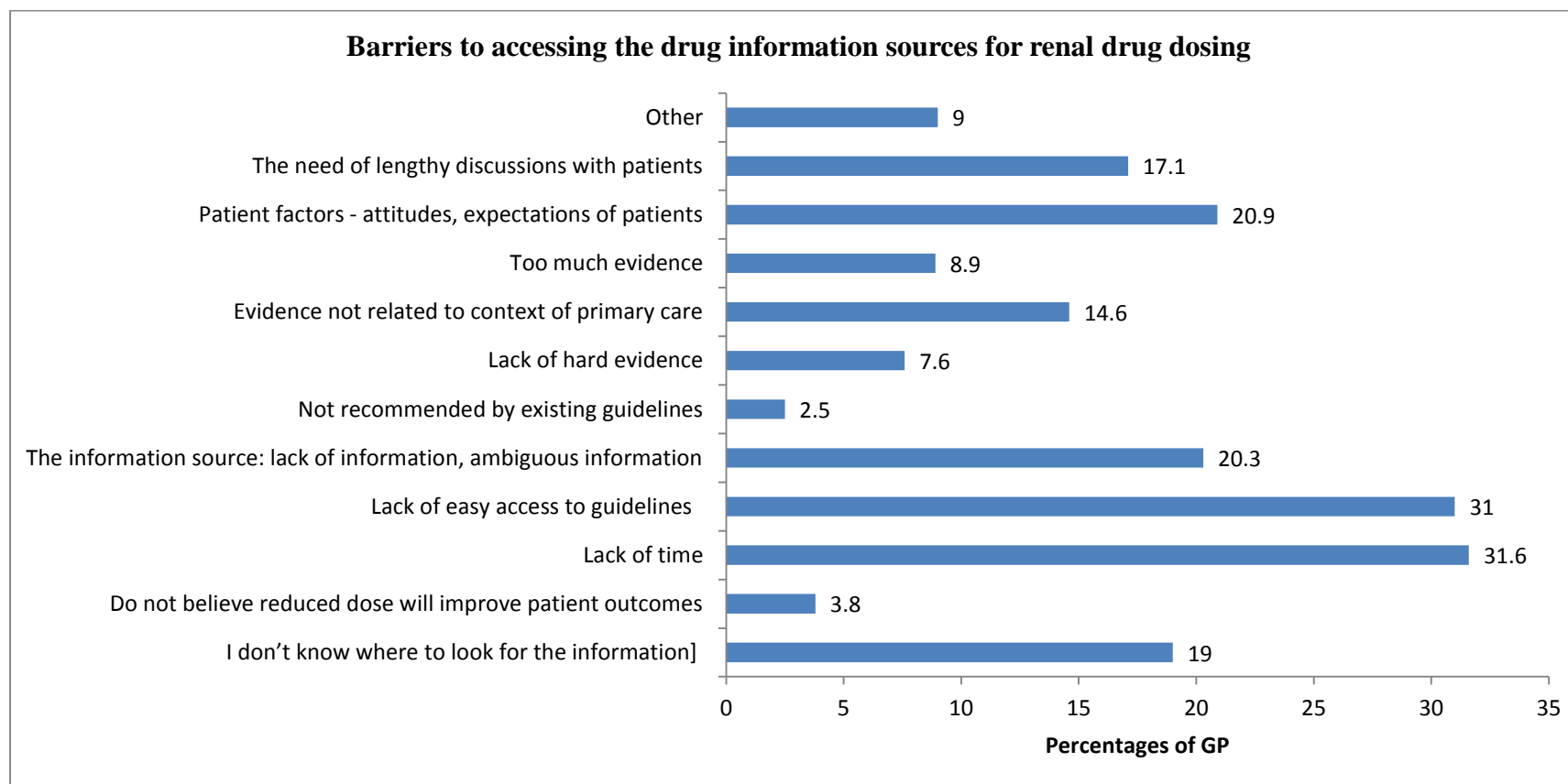


Figure 7.17 Barriers to accessing guidelines for renal dosing

7.4.1.11 Factors responsible for inappropriate prescribing

Factors responsible for inappropriate prescribing as suggested by the GPs are presented on Figure 7.18. GPs not making use of information available on drug dosing, insufficient access to dosing information during consultation, lack of awareness of availability of information sources, GPs not making use of information about individual patients and, the lack of routine renal function assessment were factors cited as contributing to inappropriate prescribing in CKD.

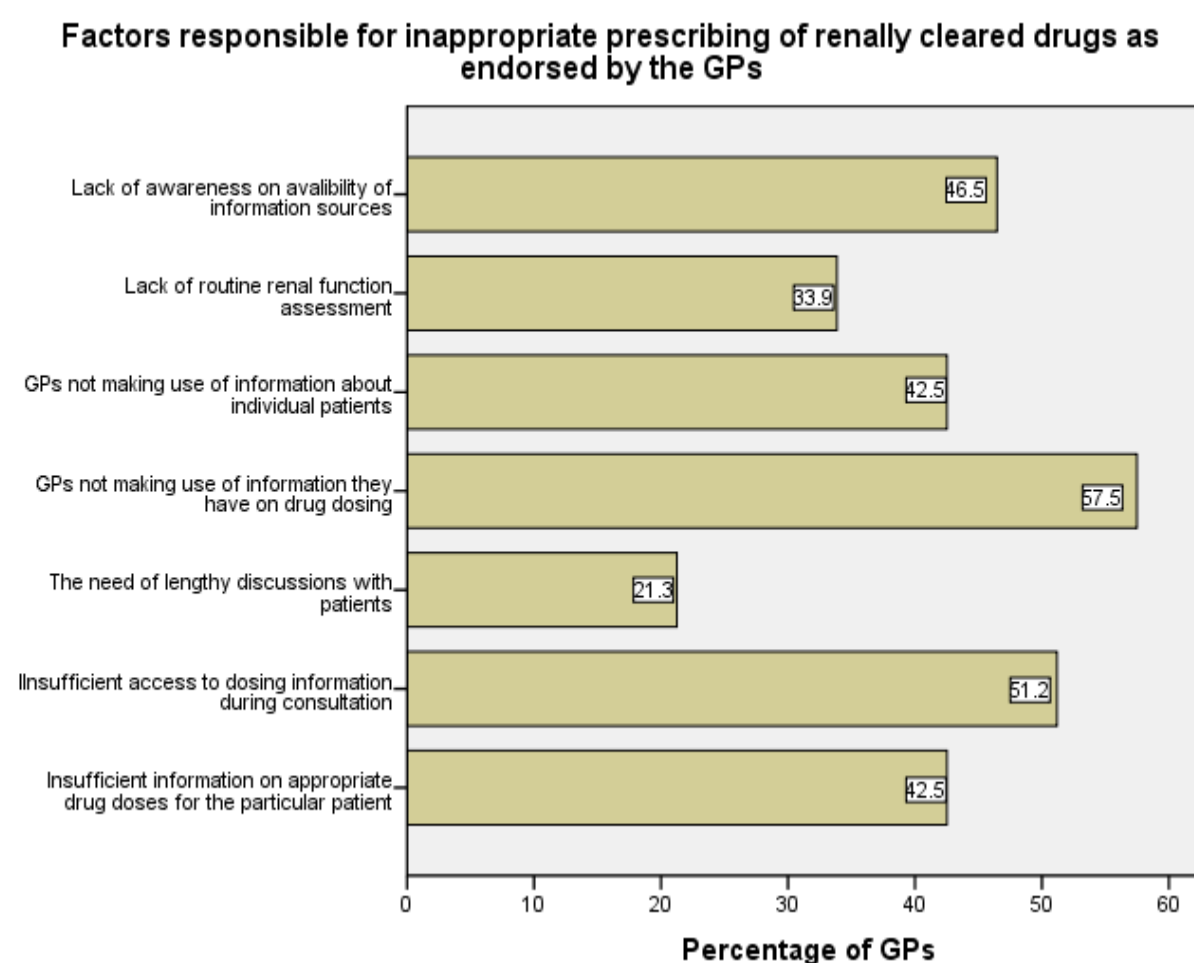


Figure 7.18 Contributors to inappropriate prescribing

7.4.1.12 Interventions to enhance optimal dosing in CKD

GPs were asked to rank the interventions that would most appeal to them to help optimise the medication for patients with CKD. Respondents' ratings for pre-specified interventions, based on means from the Likert scales, are presented on Table 7.7. The three

most desired interventions ranked by the GPs were clinical decision support system, face to face and online learning modules, and academic detailing visits by a nephrologist.

S.N.	Types of intervention	Mean (SD) rank	Rank of intervention types
1	Clinical decision support systems that assist with drug dosing decisions	2.4 (1.7)	1
2	Academic detailing visits by a nephrologist	3.3 (1.7)	3
3	Pharmacist-conducted medication reviews	3.9 (1.5)	5
4	Online training and education	3.8 (1.5)	4
5	Continuing medical education lectures	4 (1.5)	6
6	Face to face and online learning modules	3.3 (1.5)	2

Table 7.7 Interventions to optimise dosing in CKD

N=125, Ranked by Mean Rank Order, Rank score ranges from 1 to 6, (1: most important, 5: least important)

7.5 Discussion

The results of our study highlight the barriers to GPs ordering routine kidney function tests and using the guidelines and information sources for optimal dosing in patients with CKD. This study informs the areas where interventions need to occur to address these barriers and help identify the choice of interventions likely to be most effective. Previous overseas studies have demonstrated a knowledge gap and subsequent suboptimal CKD management practices among the GPs in the primary care settings.¹⁶⁻¹⁹ Lack of awareness of CKD guidelines, less accurate diagnostic procedures, low confidence of GPs, limited educational and administrative resources for CKD management, desire for more CKD practice guidance, and a lack of awareness of eGFR and its correct usage, were some of the observations noted from these studies.^{18 20-22 23 24}

The GPs included in our study expressed similar comments. Our findings elaborate more upon the results of these studies by examining factors beyond those of GPs' knowledge and understanding, to identify system-level, practice-level confounding factors that serve as barriers to implementing available evidence-based guidelines for prescribing in patients with

CKD. In contrast, the GPs in our study demonstrated more awareness towards the use of eGFR as an indicator of kidney disease and often stated using it for drug dosing purposes.

Overall, our results support those of other studies that indicate continued low awareness of CKD management guidelines, uncertainty around acceptable renal function tests, confusion surrounding the most correct test for renal dosing and a desire for intervention programs to improve CKD care. Additionally, the GPs expressed concerns over the inadequate and ambiguous renal dosing recommendations included in the drug information sources. Furthermore, time constraints, fears of over-servicing, risk of over diagnosis associated with automated eGFR, practitioner's inertia and the logistics of getting a test before prescribing, were some of the challenges to ordering a kidney function test.

In an online survey of GPs, George *et al* reported lack of confidence as one of the main barriers to the management of CKD in primary care.¹⁸ Similarly, GPs in our study reported low confidence in identifying nephrotoxic and renally-cleared drugs while prescribing for patients with CKD. GPs also demonstrated varying opinions on the usage or avoidance of drugs such as bisphosphonates, ACE-inhibitors and metformin in renal impairment. Contributing factors could be the inconsistent and inadequate recommendation regarding their dosing across the standard information sources and the contradictory information pertaining to their use or avoidance in CKD in the literature.²⁴¹ Educational interventions have been found to be effective in improving the level of confidence of GPs in CKD management.²⁶⁶

The AusHeart study has concluded that CKD is common, significantly under-recognised and under-treated in primary care.²⁶⁷ In rural general practice in Australia, there are significant shortfalls in the recording of kidney function.²⁶⁸ The national survey of Australian GPs has shown that 50% of patients attending general practice have undergone a kidney function test in the previous 12 months.²⁶⁹ The most frequent barriers to ordering a kidney function test, recognised by the GPs in our study were- limited time or more urgent patient issues, fear of over-servicing and the associated cost. The recent decision by the Federal Department of Health and Ageing to include the measure of kidney function as a part of the GP Practice Incentive Payment could potentially resolve some of the barriers. GPs expressed discomfort in discussing early CKD and the need for dosage adjustment with patients due to the potential risk of provoking concern in patients by labelling their declined renal function as kidney disease. This discomfort could be resolved by including CKD care in discussion of

diabetes or hypertensive care and sharing the responsibility of reassuring patients with other practice staff.²⁶²

We found that the GPs had favourable views towards the automated eGFR reporting and this was consistent with results from other studies.^{270 271} GPs demonstrated more awareness of eGFR as an indicator of CKD, often listing it as a preferred tool for renal dosing purposes. This aligns with the recent recommendation from the Australasian Creatinine Consensus in using the eGFR calculated with the MDRD formula for drug dosing decisions in general practice for non-critical-dose drugs.¹⁰⁶ Easy availability, enhanced detection and better accuracy has made automated eGFR a preferred choice for renal dosing in general practice.²⁷² However, caution is required while using eGFR for drug dosing. Dosage adjustment in specific patients, such as the elderly or those in extremes of body weight, need consideration for body surface area.²⁷³ Interventions aimed at providing more information in regards to usage and interpretation of eGFR values would seem appropriate.

There was less familiarity with the Kidney Health Australia guideline among the GPs and some of the GPs expressed that it was not very helpful in the primary care setting. Studies overseas have documented GPs lack of awareness of CKD management guidelines.^{18 19} Deficiencies in knowledge regarding the CKD management guidelines was identified as one of the important barriers to CKD care and was the reason for suboptimal management of CKD.¹⁶ GPs who are less aware to the guidelines are less likely to recognise CKD and monitor its progression.¹⁶

Limited awareness to CKD guidelines might be due to the reason that these guidelines are relatively newer and are lesser publicised than hypertension or diabetes guidelines.²¹ Some CKD management guidelines, such as KDOQI guidelines, are cumbersome to read and competing demands create difficulty for GPs to access practical elements during patient consultation.²⁷⁴ Due to lack of awareness about existing CKD guidelines, GPs largely rely upon evidence-based diabetes and hypertension guidelines to manage the CKD.²³ Continuing medical education has been suggested to overcome the knowledge gap of GPs in the identification and medication management in CKD.¹⁷

GPs have embraced the electronic resources to a greater extent than paper-based resources. The time taken to navigate was the main barrier to accessing the electronic sources. Information source preferences were consistent between rural and non-rural GPs. These findings are in concordance with previous studies.^{275 276} There was a general scepticism

expressed concerning the usefulness, reliability, and applicability of the information sources. MIMS/Product information was the most commonly used information source for renal dosing. Despite being the one of the most frequently consulted drug information sources in Australia, MIMS has been found to suggest an altered dosage regimen without a quantifiable measure of renal function for renally-cleared drugs.¹⁷⁸

The majority of the GPs said they have difficulty in adjusting dose in CKD patients. Lack of easy access to guidelines, lack of time, ambiguous information, and evidence not related to the context of primary care, limited their use of the guidelines. In our study, 21% of GPs still believed in renal dosing based of serum creatinine level. A similar result was found in general practices overseas.¹⁷ Although used in daily practice, it is inappropriate to use serum creatinine level in isolation for screening renal function, particularly in the elderly.⁸⁷ This reliance on serum creatinine level leads to underestimation of renal impairment and subsequently contributes to incorrect prescribing.

The challenges implied by the results of our study require an innovative approach to optimise dosing in patients with CKD. Addressing the barriers to using the guidelines with concrete interventions at the levels at which they occur would help to improve the dosing in patients with CKD. Insufficient and ambiguous information in drug information sources to guide the dosing has been pointed out at various times.^{177 193} There is a need for the drug information providers to present the renal dosing information in an unambiguous format so that the GPs can easily incorporate them into their daily practice. Guidelines with clear non-controversial and evidence recommendations are more likely to be employed than guidelines with recommendations that are unclear, controversial or based on opinion.²⁷⁷

Lack of awareness about available information sources and skills to access them can be improved by systematic educational intervention. A series of brief, individualised training sessions on available sources and updated information on renal dosing could help develop accessing information skills. The significant time to seek information coupled with a need to consult multiple sources, each with a varying design and interface, is a potential barrier to drug dosing which could be addressed through the use of a tool, integrating multiple sources into a single interface. This would allow access to multiple sources without the need to extensively search and could provide information from each individual source. Continued online medical education focusing on updated information can potentially address the confusion associated with the existing practice of using different formulae for different purposes.

A decision support system incorporated within the prescribing software that could alert the provider to order a serum creatinine test may be beneficial. The alert could also provide references to guidelines and studies that informed these guidelines. Studies are needed to understand if such interventions could improve dosing without substantial economic impacts or disrupting the general practice workflow.

7.6 Conclusion

Addressing the barriers to using the guidelines with concrete interventions at the level at which they occur to ultimately improve the dosing in patients with CKD, is warranted. Updating the information sources to present the key elements in an unambiguous format in conjunction with efforts to build consensus among the standard information sources seems necessary. As a result, GPs can incorporate the recommendations into practice. Improved dissemination of existing guidelines, online education to increase awareness on drug dosing, available guidelines and how to use them, and decision support systems to aid GPs in identifying renally-cleared drugs, appear warranted.

7.7 Next step

Inappropriate prescribing increases the risk of adverse drug events and can lead to morbidity, increased hospitalisation along with an excessive healthcare utilisation and substantial economic burden.^{126 154} The majority of these adverse drug events occur as a result of medication dosing error and are predictable and often preventable. Preventable adverse drug events often occur as a result of medication dosing errors.¹⁹² Prescribing errors can occur because the prescribers do not have immediate access to the updated information related to the drugs.²⁷⁸ The problem of dose inappropriateness can be addressed to some extent by general education and by raised awareness of medications requiring dosage adjustment and, the need for routine assessment of renal function.¹² Clinical pharmacist dosing services, reinforced by an immediate concurrent feedback strategy implemented by the clinical pharmacist, improved the dosing of renally-cleared drugs, lowered the rate of adverse drug events, reduced the cost and improved the overall delivery of healthcare.^{129 279 280}

Computerised dosing programmes have increased the proportion of doses of renally eliminated drugs adjusted to renal functions, decreased drug costs and, have the potential to

prevent adverse drug events.²⁷⁸ Pharmacist-conducted medication reviews have been found to be effective in reducing the use of potentially inappropriate medicine for elderly people in Australian community settings.¹³⁹ It seems that pharmacist involvement in medication management and online education and training programs in the community settings is warranted to avoid the unwanted effects of drugs. This ensures optimal patient outcomes and improve the quality of healthcare delivered to patients. Based on this background, in the next phase, we conducted a systematic review on studies that examined the interventions provided by pharmacists in patients with CKD and determined the outcomes.

Chapter 8 TYPES AND NATURE OF PHARMACIST MEDIATED INTERVENTIONS AND THE OUTCOMES IN CKD-A SYSTEMATIC REVIEW

8.1 Chapter Introduction

This chapter presents a systematic review to examine the published literature to recognise and appraise the outcomes that can be influenced by pharmacists' interventions in the management of patients with CKD.

The scope of the review was broadened by the inclusion of studies on patients with ESRD in addition to studies performed on patients with mild and moderate CKD. This is because the NKF-KDOQI guideline explicitly highlights the need for routine pharmaceutical care at all stages of CKD. This includes conducting regular medication reviews, dose monitoring, therapeutic drug monitoring, and detection of adverse drug reactions. There are five stages of CKD based on GFR values: at risk (>90 mL/min/1.73 m²), mild (60-89 mL/min/1.73 m²), moderate (30-59 mL/min/1.73 m²), severe (15-29 mL/min/1.73 m²), and renal failure or ESRD (GFR <15 mL/min/1.73 m²). Pharmaceutical care is equally warranted at all these stages of CKD to optimise pharmacotherapy and patient care.

An additional reason for broadening the scope of the review to include ESRD patients was that drug regimens of ESRD patients are prone to frequent change and are more susceptible to drug-related problems (e.g. dosing problems and medical record discrepancies). Therefore, intensified care and additional monitoring is warranted for these patients. For example, patients with ESRD undergoing dialysis are prescribed an average of 12 medications and present around six comorbidities. Patients who have undergone a renal transplant are also required to take a multitude of drugs and adherence to these medications is essential to avoid graft rejection and medical costs. Given the complexity of dosing and changes in drug pharmacodynamics and pharmacokinetics, pharmacist provided intervention is imperative for these patients.

The broadening of the scope of the review aligns with the overall aim of the thesis: to determine how to improve the use of high-risk medications in patients with CKD. Initially, we quantified the extent of inappropriate prescribing in CKD patients at all stages of severity, through examination of HMR and RMMR cases. Later, through the online survey, we established pharmacist intervention as one of the preferred methods for GPs to ensure correct dosing and optimal management of CKD. The management of CKD is multifaceted and includes the management of comorbidities, drug dose monitoring, and patient education. As pharmacotherapy experts, pharmacists are indispensable for these tasks. Given the aim of this

chapter is to determine the type of interventions conducted by pharmacists in terms of the management of CKD, it is additionally necessary to include ESRD patients. This is particularly the case because the management of CKD is a continuous process starting from the early stages and continues for ESRD patients both with and without dialysis and transplant.

8.2 Introduction

With the growing prevalence of chronic renal impairment worldwide, the number of patients developing end stage renal disease (ESRD) and undergoing dialysis or receiving renal replacement therapy is increasing every year.²⁸¹ Opportunity exists for involvement by pharmacists in all stages of chronic kidney disease (CKD), from diagnosis to ESRD. In general, CKD is associated with various comorbidities and complications that require multiple medications.^{282 283} A dialysis patient on average receives 10 prescription drugs and 2 non-prescriptions drugs.²⁴² Drug-related problems (DRPs) are frequent in patients with CKD and special attention should be given towards their identification, prevention and resolution.¹⁸⁷ The higher prevalence of DRPs, frequent occurrence of adverse drug events^{190 284} and patients' non-adherence²⁸⁵ requires the active involvement of pharmacists in renal disease management, as the task of drug use monitoring and controlling cannot be performed by a single health professional and requires a multidisciplinary approach. Pharmaceutical care programs involving multidisciplinary health care teams have proven to be very effective in the management of chronic illnesses like hypertension²⁸⁶, asthma²⁸⁷, diabetes²⁸⁸ and hyperlipidaemia²⁸⁹. Significant gaps in regards to optimal pharmacotherapy, adherence, referral to nephrologist and management of comorbidities in patients with CKD have been reported in various studies, and these may be subject to interventions by pharmacists.^{180 290}

This systematic review aims to examine the published literature to recognise and appraise the outcomes that can be influenced by pharmacists' interventions in the management of patients with CKD in various settings. Two specific questions directed the review:

- What are the types of interventions provided by pharmacists in patients with renal disease?
- What is the effect of these interventions in patients with renal disease?

In this review the term ‘intervention’ refers to any action undertaken by the pharmacist with the aim to improve the therapeutic outcomes in the patients.

8.3 Methodology

8.3.1 Design and study selection

A literature search was conducted according to the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) to review the available literature on the effect of pharmaceutical care in patients with chronic kidney disease.²⁹¹ Five databases (*PubMed, International Pharmaceutical Abstracts, Embase, CINAHL and Cochrane*) were searched for relevant articles in January 2015 without time limits.

Inclusion criteria for this systematic review were studies addressing:

- Interventions provided by pharmacists or pharmacists as a part of a team.
- Interventions provided through a pharmacy-based decision support system.
- All type of studies including controlled (randomised and non-randomised) and uncontrolled trials (observational studies).
- Results published in abstract form (e.g. congress abstract) were included if they provide information on interventions and outcomes.
- Studies done in all range of settings (hospital ward, ambulatory, transplant clinics).

Exclusion criteria for the review were:

- Studies in a language other than English.
- Review articles or case reports.
- Studies that did not report the nature of the intervention(s).
- Studies that did not report the outcomes of the intervention(s).

Search strategy: The following queries were used in the databases to identify the relevant articles.

PubMed (“Pharmacists” [Mesh] OR “Pharmaceutical Services”[Mesh] OR “Community Pharmacy Services”[Mesh] OR “Pharmacy Service, Hospital”[Mesh] OR “Pharmaceutical Services, online” [Mesh]) AND (“Kidney Failure, Chronic”[Mesh] OR “Renal Insufficiency, Chronic”[Mesh] OR “Renal Dialysis”[Mesh] OR “Renal Replacement Therapy”[Mesh])

International Pharmaceutical Abstracts ("Clinical pharmacy" OR "pharmaceutical care" OR "Pharmacist" OR "Hospital Pharmacy") AND ("chronic renal disease" OR "renal insufficiency" OR "dialysis" OR "renal transplant" OR "renal replacement therapy")

CINAHL ("Clinical pharmacy" OR "pharmaceutical care" OR "Pharmacist" OR "Hospital Pharmacy") AND ("chronic renal disease" OR "renal insufficiency" OR "dialysis" OR "renal transplant" OR "renal replacement therapy")

Embase 'Clinical pharmacy'/exp OR 'pharmaceutical care'/exp OR 'pharmacist'/exp OR 'hospital pharmacy'/exp AND ('renal insufficiency'/exp OR 'kidney'/exp OR 'renal replacement therapy'/exp)

Cochrane Pharmacist AND Kidney/Renal

Additionally, the reference sections of the publications were screened manually for other relevant articles.

8.3.2 Data extraction

Data in relation to predefined parameters including study design, year of publication, country, duration, setting, aim, characteristics of patients, type of interventions and outcomes, were extracted.

8.4 Results

A total of 1093 records were obtained from the various databases. After removing the duplicates, 994 articles were retrieved for further evaluation. Among the retrieved articles, a total of 802 articles were excluded by title screening. The full texts of the remaining 192 articles were assessed for eligibility and 122 studies were excluded. The predominant reasons for exclusion were a) articles not mentioning any intervention performed by pharmacists in patients with CKD and b) articles without a method or result section. Finally, 74 articles were included in the review after adding four articles identified from reference lists. A total of 15 studies were available as abstracts.²⁹²⁻³⁰⁶ The diagrammatic representation of the search process is shown in figure 9.1.

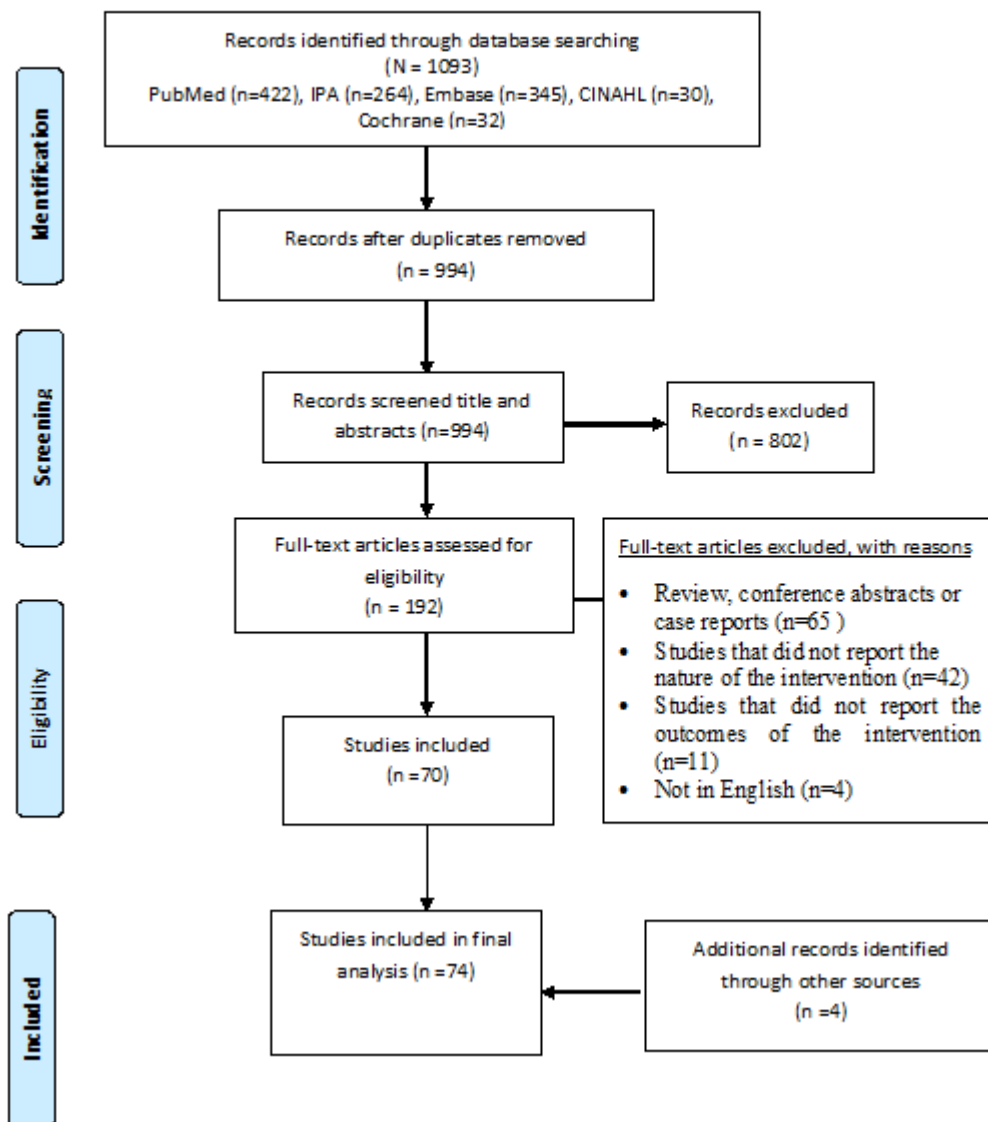


Figure 8.1 Search strategy

8.4.1 Study Characteristics

The majority of the studies were conducted in the hospital outpatient (ambulatory) setting (n=39), followed by 25 in inpatients, 5 in the community, 1 in both ambulatory and inpatients, 3 in renal transplant clinics, and 1 in a dialysis centre. Most of the studies had an uncontrolled design. There were 8 prospective non-randomised controlled, 40 prospective uncontrolled, 2 retrospective controlled, 7 retrospective uncontrolled, 13 prospective randomised controlled and 4 historical controlled. The studies were carried out in the USA

(n=44), Canada=1, Europe (n=13) and Asia (n=16). In terms of participants, 26 studies were conducted in haemodialysis patients (HD), 32 in CKD, 10 in transplant patients, 6 in dialysis (HD and peritoneal dialysis; PD) patients.

The mean sample size varied greatly from a minimum of 23 participants to maximum of 2002 participants (excluding the studies that used the decision support system as a means of intervention). The sample size for the studies involving decision support ranged from 17,828 to 51,877 participants. Eight studies did not report the sample size.^{292 295 297 299 301 303 307 308} Pharmaceutical care activities in patients with CKD indicated an increasing trend with the year. (Pearson correlation=0.6, $P<0.01$) Figure 8.2.

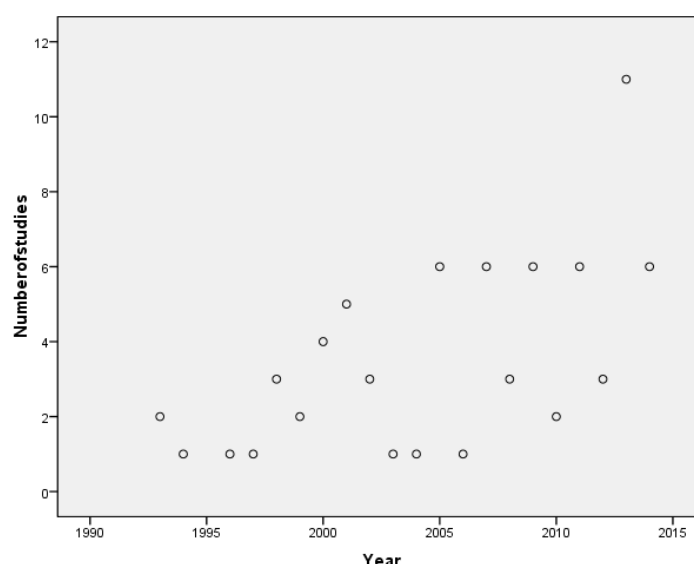


Figure 8.2 Studies focusing on pharmaceutical intervention in patients with CKD per year

The interventions performed by pharmacists in the included studies could be categorised into: Pharmaceutical care services with primary focus on (Figure 8.3)

1. Management of co-morbidities and complications (n=27, 37.8%)
2. Optimisation of drug therapy (n=39, 51.3%)
3. Educational activities (n=8, 10.8%).

The types of outcomes observed and key measurements of such outcomes used in the studies were grouped as follows.

- Clinical/physiological outcomes: This included the change in the physiological, biochemical and disease-related parameters in the patients as a result of intervention. The key measurements of such outcomes were levels of haemoglobin, glycosylated haemoglobin, triglycerides, cholesterol, parathyroid hormone, serum creatinine, systolic blood pressure, diastolic blood pressure, blood glucose, length of hospital stay, hospitalisation rate and occurrence of adverse events etc.
- Humanistic outcomes: This included change in behavioural parameters as a result of intervention. The key measurement parameters of such outcomes were:
 - Patient (knowledge, awareness, quality of life, adherence)
 - Physician (acceptance of recommendation)
- Drug-related outcomes: drug therapy appropriateness, dosing error.
- Economic outcomes: Cost saving

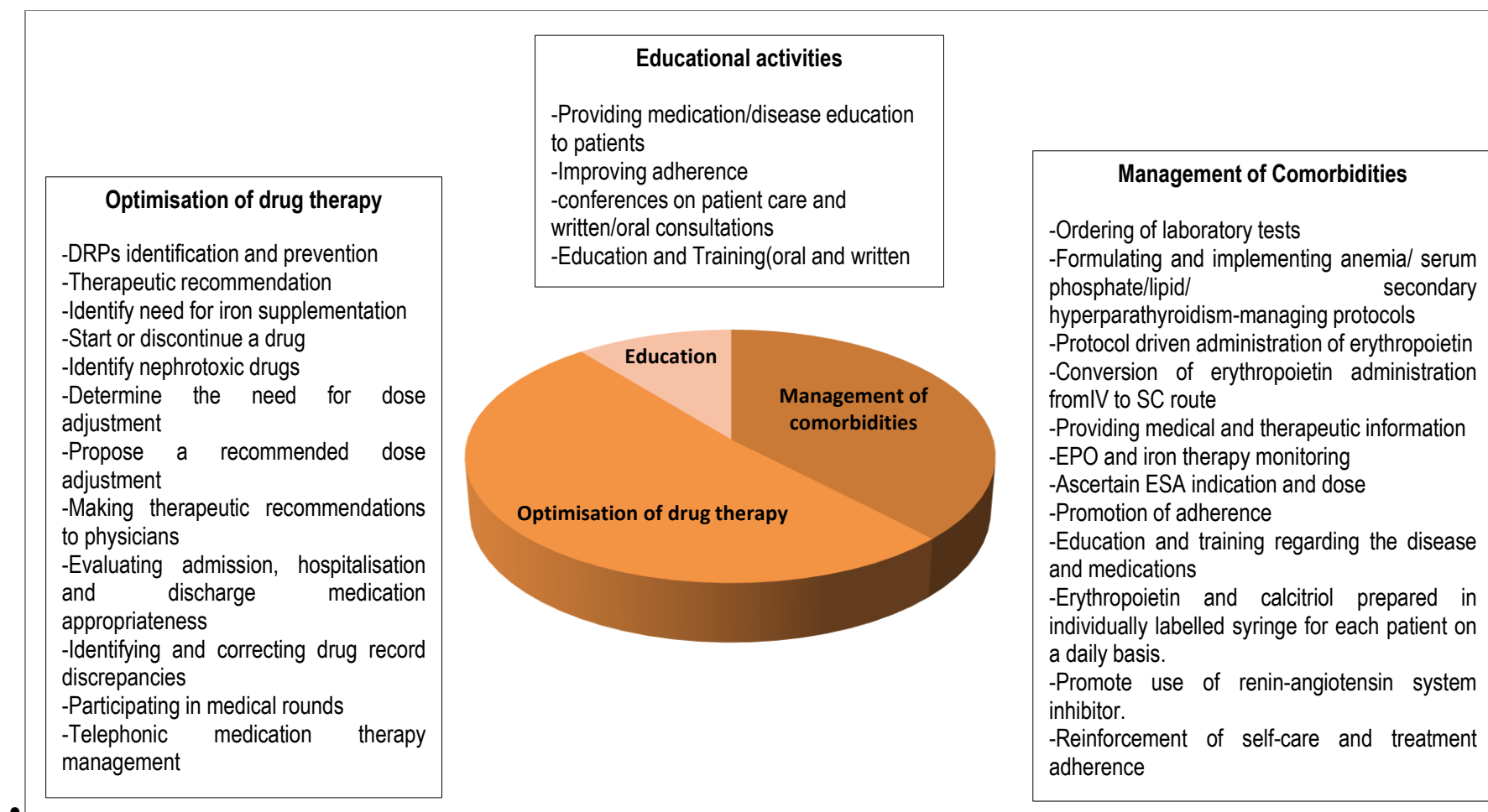


Figure 8.3 Nature and type of pharmaceutical interventions in patients with CKD

8.4.2 Types and the nature of pharmacist's interventions

Pharmacist intervention-optimal management of co-morbidities and complications

The most common co-morbidities and complications of CKD managed by pharmacists were anaemia,^{214 225 292 295 299 303 304 307 309-314} hyperlipidaemia,^{294 315} diabetes,^{301 316} hypertension,^{317 318} hyperphosphatemia³¹⁹ and hypocalcaemia.³¹⁹ Pharmacists were primarily responsible for implementing disease management protocols, drug dosing protocols and providing therapeutic information to physicians. Pharmacists were also involved in developing and implementing a phosphate management protocol²¹⁰, managing infections³²⁰ and ulcers in patients with CKD²¹⁸. Comprehensive comorbidity management programs in some studies included managing independent dosing and dose modification of erythropoietin and iron therapy.^{214 295 299 303-305 307 311 321 322} Pharmacists were primarily involved in counselling the patients regarding disease/drug/dietary therapy and implementation of adherence-enhancing activities such as training regarding device use and erythropoietin administration methods. Pharmacists performed medication reviews and provided therapeutic recommendations to physicians. Few studies gave special attention towards monitoring and adjusting the dose of darbopoietin.^{225 304} Apart from this, the pharmacists were involved in providing information to physicians in renal anaemia.³¹⁰

Table 8.1 Intervention focused on the optimal management of comorbidities in CKD

Reference Year Author	Patient characteristic s N(C/T) Age (Years) Mean (SD)	Study design/ Setting	Aim	Duration (months)	Intervention	Key measurements	Outcomes of intervention/Result
Allenet (2007) France	14 Dialysis 11 TP 52.3 (15.4)	Prospective uncontrolled Ambulatory	Assessment of a pharmacist run anaemia education program for patients with CKD.	3	-Education and training (medical and therapeutic information)	-Hb Level -Adherence	-High level of patient adherence achieved with an optimal haemoglobin level within two months.
Kimura (2004) Japan	45 HD NM	Prospective uncontrolled Ambulatory	Evaluation of the impact of pharmacist run anaemia management program for the ESRD patients.	9	-Education and training (drug information to physician on renal anaemia) -Dose monitoring and adjustment -DUE and therapeutic recommendations	-HCT level	-Increased trend of mean HCT and number of patients with HCT >30%.
Millitello (2010) USA	NM HD	Prospective uncontrolled Ambulatory	A pharmacist-driven team approach to anaemia management in	NM	-Dose monitoring and adjustment	-No. of patients with target Hb level	-Increase in number of patients within the Hb target

			an outpatient dialysis unit.		(EPO and iron therapy monitoring)		range (10-12 g/dl) from 50% to 70%.
To LL (2001) USA	49 HD 60(12)	Retrospective uncontrolled Ambulatory	Comparison of a pharmacist run anaemia management program with physician based anaemia management program in a Veterans dialysis centre.	6	-Dose monitoring and adjustment (EPO, iron therapy monitoring)	-HCT level -Tsats -Iron dose	-No significant changes after intervention in • HCT[mean(SD) 35.36(3.33) vs 36.21(3.46)] • Tsats [mean(SD) 29.82 (14.92) vs 30.78(13.17)] -Reduction in dose of elemental iron.
Walton (2005) USA	278 HD 46.2(13.4)	Prospective uncontrolled Ambulatory	Assessment of pharmacist managed anaemia program in a HD clinic.	6	-Dose monitoring and adjustment (epoetin and iron therapy monitoring)	-Hb level -Ferritin -Tsats	-Significant elevation after intervention in • Hb level (9.5 vs11.8 g/dl) • Ferritin [mean(SD) 280.9 (326.4) vs 431(22.1)] • Tsats [mean(SD) 21(7.9) vs 33(8)] -Increase in number of patients with Hb>11 g/dl.
Bucaloiu (2007) USA	134 CKD (62/74) NM	Prospective controlled Ambulatory	Assessment of the effect of a pharmacist driven anaemia management in patients with CKD	32	-Dose monitoring and adjustment (protocol driven administration of erythropoietin)	-Hb level - Tsats	-Pharmacist managed group maintained higher percentage of Hb and Tsats value and achieved the goal Hb level

			compared with the physician managed group.				faster than physician managed group
							<ul style="list-style-type: none"> • Hb (mean 69.8 vs 43.9%) • Tsat (mean 64.8 vs 40.4%) • Time (47.5 vs 62.5 days)
Quercia (2001) USA	NM HD NM	Prospective uncontrolled Ambulatory	Evaluation of cost avoidance and clinical benefits derived from a pharmacy managed anaemia program.	1995, 1998	-Dose monitoring and adjustment (EPO and iron dose monitoring) -Formulation of anaemia management protocol	-Level of HCT -Cost avoidance	-Significant cost avoidance in EPO from 1995-1998 (estimated \$1018638). -Decrease in number of patients with HCT < 31% (32% in 1994 to 14% in 1998).
Joy (2007) USA	166 CKD NM	Prospective uncontrolled Ambulatory	Assessment of the effect of a clinical pharmacist managed anaemia programs.	28	-Dose monitoring and adjustment (darbopoietin)	-No. of patients achieving target Hb	-Increase in no. of patients with Hb target range (41% vs 78%).
Brown (2007) USA	190 (73/117) CKD	Retrospective controlled Ambulatory	To determine clinical significance and cost effectiveness of pharmacist-run EPO Clinic.		-Dose monitoring and adjustment (darbopoietin and epoetin)	-No of patients achieving goal Hb level -Cost of therapy	-92% of patients in EPO clinic and 69% of patients in control group achieved goal haemoglobin level. -Cost saving in EPO clinic patients.
Buenviaje (2000)	HD	Prospective	Comparison of pharmacist managed	3 month	-Medication review -Dose adjustment	-HCT level -EPO dose	-No significant difference between the protocol group

USA		uncontrolled Ambulatory	anaemia program to physician based anaemia management.			-Total iron dose -Mean T _{sat}	and the physician managed group in <ul style="list-style-type: none"> • Mean HCT level (36.2% versus 35.4%) • Total EPO dose (7.7 million units versus 8.5 million units) • Oral iron dose (95,550 mg versus 85,605 mg, P=0.638) • Mean TSAT (30.78% versus 29.82%, P=0.66). -Higher use of IV Fe in physician managed group.
Qin (1998) USA	NM	Prospective uncontrolled Ambulatory	To determine the impact of pharmacy services in decreasing EPO usage while avoiding anaemia of ESRD.	NM	-EPO dose monitoring	-HCT level -Cost reduction	-Significant improvement in HCT -Reduction in EPO dose per treatment -Cost avoidance of \$184,000 annually.
Ueoka (2000) USA	HD	Prospective uncontrolled Ambulatory	To improve patient outcomes while reducing the total weekly dose of	24	-Dose monitoring and adjustment	-Dose reduction -HCT level	-Average weekly erythropoietin dose reduced by 31%.

			erythropoietin through establishing the clinical pharmacist role in providing consistent assessment and dose adjustment.		-Conversion of erythropoietin administration from the IV to the SC route.		-Mean HCT maintained in the range of 32 to 36%.
Anonymous (1998) USA	160 HD (1996) 175 HD (1997) NM	Prospective uncontrolled Inpatients	Assessment of pharmacist management of hypocalcaemia and hyperphosphatemia.	12	-Dose monitoring and adjustment (preparation of IV calcitriol by pharmacist for each patient on a daily basis)	-No. of patients with the disease conditions	-Significant decrease in no. of patients with moderate to severe hyperparathyroidism [mean (SD) 12 (7) vs 23 (14)].
Yokum (2008) UK	34 (17/17) HD 51.1(12.7) 47.6(14.4)	Randomised controlled Ambulatory	Evaluation of a phosphate management protocol designed to achieve optimum serum phosphate levels in HD patients.	4	-Patient education and training (medication and disease) -Serum phosphate management protocol	-Serum phosphate level	-Reduction in serum phosphate level [mean (SD) 1.81 (0.54) Vs 2.07 (0.25) mmol/L. -No change in parathyroid hormone level.
Chisholm (2002) USA	23 (10/13) TP 47(12.7) 51(16.8)	Randomized controlled Transplant clinic	Assessment of difference in BP control between the renal transplant patients with or without pharmaceutical care.	12	-Medication Review (Identifying, preventing and resolving DRPs) -Education and training	-SBP and DBP level	-Reduction in mean SBP and DBP in intervention group at the second, third and fourth quarter of the study.

					-Therapeutic recommendations -Promotion of adherence		
Chisholm (1999) USA	33 (15/18) TP NM	Randomized controlled Transplant clinic	Evaluation of effect of pharmaceutical care services on renal transplant patients' blood glucose levels.	12	-Medication review (Identifying, preventing and resolving DRPs) -Therapeutic recommendations	-FBG level	-Reduction in the FBG level in the intervention group.
Shaffer (2003) USA	285 dialysis NM	Prospective uncontrolled Dialysis centre	To develop a dialysis unit protocol to improve dyslipidaemia control and to increase provider awareness	2	-Ordering and assessment of lipid level. -Therapeutic recommendations to providers	-Total cholesterol -LDL-C	-Reductions in total cholesterol and LDL -Increase in the rate of lipid panel labs and statins order. -Increase in provider awareness.
Viola (2002) USA	26 HD 55.7 (11)	Prospective uncontrolled Ambulatory	Assessment of the effectiveness of a multidisciplinary lipid management program.	6	-Dose monitoring and adjustment -Laboratory test order -Patient education and training (medication counselling)	-LDL-C -HDL-C -Total cholesterol	-Significant reduction after intervention in <ul style="list-style-type: none"> • LDL [mean (SD) 80 (3) vs 96 (5) mg/dL • Cholesterol [mean (SD) 151 (4) vs 170 (7) mg/dL

							-Increase in no. of patients reaching target LDL (88 versus 58%)
Leal (2008) USA	601 CKD 57.7 (13.5)	Prospective uncontrolled Community	To evaluate a pharmacist based disease state management service	NM	-Dose monitoring and adjustment -Education and training (disease and medications)	-HbA _{1C} level -BP -Cholesterol	-Increase in number of patients at target goals for BP, HbA _{1C} and cholesterol receiving aspirin and angiotensin converting enzyme inhibitor.
Abrahams 2005 USA	140 HD NM	Retrospective uncontrolled Ambulatory	To evaluate the effect of pharmacy managed collaborative program to optimally manage anaemia and secondary hyperparathyroidism	10 years	-Drug use evaluation -Dose monitoring -Erythropoietin and calcitriol prepared individually labelled syringe.	-Cost saving -No. of patients achieving target Hb	-Cost avoidance of over \$250,000 annually -Increase in the number of patients within the target haematocrit range of 31 % to 36%.
Aspinall (2012) USA	91/314 CKD 78.4 (8.8) 73.9 (10.9)	Historical control Ambulatory	Impact of pharmacist-managed ESA clinics for patients with non-dialysis-dependent CKD	6	-Dose monitoring and adjustment (ascertain ESA indication and dose)	-No. of patients achieving target Hb level	-More number of patients achieved target Hb range in pharmacist-managed ESA clinics (71.1% vs 56.9% for usual-care sites (P < 0.001).
Santschi (2011) Canada	89 (41/48) CKD 73.3 (7.7)	Randomised controlled Community	-Evaluate the impact of ProFiL, (collaborative and multidisciplinary	6	-Medication review (identify DRPs)		-ProFiL patients had a larger reduction in systolic BP than

	71.9 (10.4)		care programme) on management of hypertension treatment in patients with CKD		-Therapeutic recommendations to physician		the usual care group. (-4.7 mmHg vs -0.4 mmHg).
Nasution (2013) Indonesia	143 (80/63) CKD 47.06 (13.80) 49.44 (13.08)	Prospective controlled Inpatient	To evaluate the clinical and economic impacts of clinical pharmacy education (CPE) on infection management among patients with CKD	6	-Education and training Health providers were given clinical pharmacy education (CPE) on dose adjustment according to the level of kidney, identifying drug-related problems.	-Number of lives saved/100 patients treated. -Cost-effectiveness ratios for patients with CPE and without CPE	-Treatment of CKD was more effective with CPE (CKD stage 4, 88.89; CKD stage 5, 65.45) than without CPE (CKD stage 4- 78.57; CKD stage 5-57.58). -Treatment of CKD was more cost-effective with CPE compared with treatment of without CPE
Mousavi (2013) Iran	Pre-intervention: 375 Post-intervention- 236 CKD 51.2 (18.3) 50.2(18.8)	Prospective uncontrolled Inpatient	To assess the role of clinical pharmacists to decrease inappropriate stress ulcer prophylaxis (SUP) prescribing and related costs for these patients.	6	-Develop SUP prescribing protocol -Educational classes for medical doctors on appropriate SUP prescribing. -Provide recommendation	-Number of patients who received SUP appropriately	-Significant relative reduction in inappropriate SUP prescribing and related cost in patients with renal insufficiency by about 44% and 67% respectively.
Leung (2005)	160 (80/80) CKD	Prospective uncontrolled	To evaluate the effect of disease management	24	-Periodic laboratory assessments (BP,	-Onset of the first event of ESRD	-Structured care patients had slower rate of renal decline (P

Hong Kong	61.1 (8.8)	Ambulatory	program for patients with diabetic nephropathy on the time to onset of ESDR or all-cause death compared with usual care.		plasma glucose, HbA1c, renal function, Hb, serum Lipids) - Risk factors control -Reinforce patient adherence -Suggesting use of renin-angiotensin system inhibitors.	-Hb, LDL, < 0.032), increased use of renin-angiotensin system inhibitor, reductions in BP, LDL cholesterol -ESDR developed in 24 and 40 patients in the structured care and usual care groups respectively.
Debenito (2014)	101 (70/31)	Retrospective controlled	To evaluate the impact of a clinical pharmacy anaemia management service on adherence to monitoring guidelines, clinical outcomes, and medication utilization in patients with CKD	36	-Manage drug therapy for a given indication -Initiation or discontinuation of specified medications, -Dose adjustment and ordering appropriate laboratory tests	-Proportions of patients achieving target Hb level and number of days required to achieve target -Average weekly dose of ESA therapy and its associated cost Pharmacist-managed patients in comparison to usual care patients had improvement in -Adherence to guidelines for Hb monitoring (32.3% vs. 14.3%, P=0.049), -Iron monitoring (61.3% vs. 30.0%, P = 0.005) -Time to achieve Hb target (28 days vs 41 days, P = 0.135) -Proportion of patients achieving target Hb (96.8% vs 95.7%, P = 0.654). -Lesser epoetin alfa during the 6-month period, leading to an
USA	72.0 (13.3) 65.6 (14.1)	Ambulatory				

							annualized savings of \$1,288 per patient in drug expenditures.
Dashti (2012) Iran	86 HD Median (range) 56 (22–84)	Prospective uncontrolled Inpatients	Evaluation of the impact of clinical pharmacy services in the management of complications in HD patients.	39	-Dose adjustment and monitoring	-Hb level -Total cholesterol -LDL-C -Serum Ca and iPTH level	-Optimal range of serum Ca and iPTH level achieved in patients who initially were on suboptimal and supra optimal range. -Hb level increased in anaemic patients. -Serum ferritin reached target values in all patients. -Total cholesterol and LDL decreased to near-optimal values in dyslipidaemia patients.
Dashti (2013) USA	92 (47/45) HD 53.6 ± 15.0	Randomised controlled Inpatient	To assess the impact of pharmaceutical care on HRQoL of haemodialysis patients	6	-Medication review (identify DRPS) -Drug therapy monitoring and dose adjustment -Interview patient and care-provider to evaluate patient's medication adherence -Education and training (disease, drugs, correct administration)	Improvement in patient's quality of life	-HRQoL improved significantly from median 56.9 at the initiation of the study to 72.2 at the end of the study in the case group (P = 0.001).

-Counselling on
lifestyle modification
and nutrition
-Information booklets

Hb: Haemoglobin, CKD: Chronic kidney disease, HD: Haemodialysis, TP: Transplant patients, ESRD: End stage renal disease, HCT: Haematocrit, NM: Not mentioned, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DUE: Drug use evaluation, T_{sat}: Transferrin saturation, FBG: Fasting blood glucose, HbA_{1c}: Glycosylated haemoglobin, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TP: Transplant, EPO: Erythropoietin, DRPs: Drug-related problems, iPTH: Serum intact parathyroid hormone, EPS: Erythropoiesis-stimulating agents, HRQoL: Health-related quality of life, GFR: Glomerular filtration rate

Implementation of anaemia management program

Twelve studies reported the impact of the clinical pharmacists interventions in the management of anaemia in patients with CKD.^{214 225 292 295 299 303 304 307 309-311} Two groups of studies were identified. In the first three trials, the tested hypothesis was whether the pharmacist-driven anaemia management program, compared with a physician-managed program was associated with improved outcomes. In a non-randomised controlled trial, Bucaloiu et al³¹² found that the protocol-driven administration of erythropoietin managed by pharmacists, as opposed to physicians, resulted in a higher percentage of haemoglobin and transferrin saturation value and faster achievement of target haemoglobin level (11-12.9 mg/dl) with use of lesser dose of erythropoietin. In contrast to these findings, Buenviaje et al³⁰³ reported that there was no significant difference between the protocol managed group and physician managed group in mean haematocrit level (36.2% versus 35.4%), total EPO dose (7.7 million units versus 8.5 million units) and mean transferrin saturation level (30.78% versus 29.82%, $p=0.66$). The only difference was a higher use of intravenous iron in the physician managed group. Similarly, To et al³¹¹ reported the pharmacist-managed protocol to be equally effective as the physician managed protocol and there was no significant difference in mean haematocrit level, total erythropoietin dose and total elemental iron dose. The haematocrit level was slightly higher than the desired range of 33-36% in the pharmacist-managed group. The authors attributed this to the requirement of the minimum two-week interval for erythropoietin dosage modification; i.e. the dosage adjustments were incremental in order to prevent wide fluctuations in haematocrit level.

In nine other studies, the hypothesis that a pharmacist-conducted anaemia management program improves outcomes in patients with CKD was tested without the use of any control group. The pharmacists were primarily involved in counselling the patient regarding disease/drug/dietary therapy and implementation of adherence-enhancing activities such as training regarding device use and, erythropoietin administration methods.^{309 310} Pharmacists performed medication reviews and provided therapeutic recommendations to physicians.³¹⁰

Implementation of hyperparathyroidism management program

Two studies described the implementation and effect of pharmacist-based management of hyperparathyroidism/hypophosphatemia/hyperkalaemia in patients with CKD. Ay et al³¹⁹

used a before and after design to examine the effect of pharmacist monitoring and adjusting the dose of calcitriol on serum phosphate and parathyroid hormone in patients with CKD. Pharmacists' interventions, consisting of preparing intravenous calcitriol for each patient on a daily basis, led to a significant decrease in the number of patients with moderate to severe hyperparathyroidism [(mean (SD) 12(7) vs. 23(14)].

In a randomised controlled trial, Yokum et al²¹⁰ designed a phosphate management protocol and evaluated its effect in achieving optimum serum phosphate level in 34 haemodialysis patients. They utilised an intensive patient education program reinforced by the serum phosphate management protocol. This resulted in a reduction in serum phosphate, with mean (SD) 1.81(0.54) in control vs 2.07(0.25) mmol/L in the intervention group. However, there was no change in parathyroid hormone level.

Implementation of hypertension management program in patients with CKD

Pharmacist intervention produced a significant decrease in systolic and diastolic blood pressure, along with an increase in the number of patients reaching the target level for blood pressure.^{317 318} Chisholm et al³¹⁷ prospectively randomized renal transplant patients into an intervention group and a control group to determine if patients who received direct patient care from a clinical pharmacist had better blood pressure control compared to those who did not engage with clinical pharmacy services. The clinical pharmacy services included a clinical pharmacist performing medication reviews, with emphasis on preventing or resolving medication-related problems and providing medication recommendations. Mean systolic blood pressure and diastolic blood pressure decreased significantly in the test group.

Implementation of blood glucose management program in patients with CKD

Pharmaceutical care service in a renal transplant clinic demonstrated a positive impact on patients' blood glucose control, along with the increase in number of patients at target goals for blood pressure, glycosylated haemoglobin and cholesterol level. Chisholm et al³⁰¹ demonstrated beneficial and a statistically significant difference in fasting blood glucose level between a pharmacist (mean change of 0 mg/dl, \-/21 mg/dl, \-/40 mg/dl, and \-/44 mg/dl) and a usual care group (+7 mg/dl, +13 mg/dl, +13 mg/dl, and +20 mg/dl) for the first, second, third, and fourth quarters of the study. The pharmacist care group received pharmaceutical care

services, which included an ongoing medication review and providing appropriate pharmacotherapy recommendations.

Implementation of hyperlipidaemia management program in patients with CKD

Two studies addressed the effect of an implementation of a dyslipidaemia control program by a pharmacist in dialysis patients.^{294 315} The dyslipidaemia control program involved the clinical pharmacists conducting medication reviews, ordering/assessment of lab tests, dose optimisation and providing recommendations to the physician. This resulted in reduction in the total cholesterol level [mean (SD) 80(3) vs 96(5) mg/dl] and an increase in the number patients reaching target level for low density lipoprotein.

Overall management of multiple complications and comorbidity

Three studies investigated, tested and measured the impact of clinical pharmacy services on the management of multiple complications in haemodialysis patients - hyperlipidaemia, anaemia, and hypercalcemia/hyperparathyroidism.^{305 321 322} There was achievement of optimal serum calcium, parathyroid hormone, haemoglobin and cholesterol level etc. The cost avoidance after the implementation of program was significant.

Pharmacist intervention-optimisation of drug therapy

There were 39 studies that aimed to optimise the drug therapy in patients with CKD. There were two approaches to optimise the drug therapy a) pharmacist conducting medication reviews, drug therapy monitoring and adjustment and b) use of a decision support system. Pharmacists were primarily involved in identification, prevention and resolution of DRPs and drug therapy monitoring and adjustment.^{151 152 220 227 306 323} Other significant pharmaceutical activities conducted by the pharmacist included- participation in ward rounds³²⁴, oral and written consultations with physicians³²⁴, preparing erythropoietin unit dosage from multi dose vial in pharmacy²⁹⁷, assessing the need for adjuvant iron therapy^{293 298 324}, patient education and counselling^{302 324}, routine laboratory assessment^{298 316}, patient adherence promotion³¹⁶, and dose modifications for iron preparations.³²⁵

Five studies described the use of a computerised decision support system (CDSS) for optimising drug dose in patients with impaired renal function.^{135 308 326-328} This system assisted the drug dosing relative to the kidney function of patients. Chertow et al¹³⁵ found an increase in rates of appropriate dose by 13% and appropriate drug frequency by 24%, and a decrease in the length of stay as result of merging CDSS with a computer order entry system and the patient's electronic record. Three studies investigated the use of a decision support that alerts prescribers to the need of dose adjustment in patients with CKD.^{308 326 328} These studies demonstrated significant reductions in rate of excessive administration of drugs and fewer medications error in test groups compared to the usual care group (33% vs. 49%) after the use of the decision support system.

Reference Author Year Country	Patient characteristics N(C/T) Age (Years) Mean (SD)	Study design/ Settings	Aim	Duration (months)	Intervention	Key measurement	Result/Effect of intervention
Castelino (2011) India	308 (HD&PD) NM	Prospective uncontrolled Ambulatory and Inpatients	Evaluation of DRPs and determining the role of clinical pharmacists in preventing DRPs in renally compromised patients	9	-Medication review (DRPs identification and prevention) -Therapeutic recommendations	-PhR acceptance	-PhR accepted in 97% of cases which resulted in change in therapy in 83% of the cases.
Hassan (2009) Malaysia	163 /154 CKD 55.56 (14.15) 55.30 (14.37)	Prospective HC Ambulatory	Assessment of the impact of dose adjustment service by pharmacist in patients with CKD	8	-Dose monitoring and adjustment	-Physician adherence -No. of ADRs -Cost savings -PhR acceptance rate	-Reduction in <ul style="list-style-type: none"> Physician's nonadherence with dosing guidelines by 27.5% Number of ADRs (73 events reduced to 49 events) -Cost savings of \$2250 US -54.6% PhR accepted
Kaplan (1994) USA	30 HD 40.5	Prospective uncontrolled Ambulatory	Evaluation of the impact of a medication review program in patients with ESRD on HD	2	-Dose monitoring and adjustment	-PhR acceptance	-76% PhR accepted -70% of PhR implemented

(DRPs reported to prescribers)							
Pai (2009) USA	104 HD (57/47) 56.3 (15)/ 60.5 (14.7)	Randomised controlled/ Ambulatory	Evaluation of effect of pharmacist intervention on drug use, drug cost, hospitalization rates and DRPS	24	-Dose monitoring/adjustment	Rate of hospitalisation	-Reduction in hospitalisation [mean(SD) 1.8 (2.4) in test Vs 3.1(3.0) control]
Chisholm (2007) USA	36 TP 52.78(13.37)	Prospective uncontrolled Ambulatory	Evaluation of effects of a medication assistance program with medication therapy management on the clinical outcomes and HRQOL of renal transplants recipients	24	-Medication review (DRPs identification and prevention) -Therapeutic recommendations	- FBG -HbA1C -Triglycerides -BP -HRQOL -Number of graft rejections	-Reduction in FBG, HbA1C, LDL, cholesterol, triglycerides, BP and no. of graft rejections -Increase in no. of patients reaching target serum cyclosporine levels. -Increase in HQOL
Castro (2010) USA	60 (58HD,2PD) NM	Prospective uncontrolled Ambulatory	Assessment of outcomes of implementing a medication therapy management service for dialysis patients	6	-Medication review (MTM program)	-SBP -HB -P -Ca-P	-MTM group had improvement in level of <ul style="list-style-type: none"> • SBP from 150±22 to 144±18/ mm Hg • HbA1c from 9.2±1.6 to 9.0±2 • P from 6.2 to 5.6 mg/dl

<ul style="list-style-type: none"> • Ca-P from 56±19 to 50±16 -Non-MTM group had no improvement in all the above clinical parameters 							
Chisholm (1998) USA	NM TP	Prospective uncontrolled Transplant clinic	Evaluation of pharmaceutical activities provided by a clinical pharmacist in a renal transplant clinical settings	8	-Therapeutic recommendations	PhR acceptance rate	-95.6% PhR accepted -67.9% of PhR had a significant and 29.3% had a very significant (29.3%) impact on patient care.
Chisholm (2000) USA	201 TP NM	Prospective uncontrolled Ambulatory	Evaluation of impact of the pharmacist's interventions on patient care and physicians' prescribing decisions	18	-Medication review (DRPs identification and prevention) -Therapeutic recommendations	-PhR acceptance rate	-Out of 844 PhR made for 201 patients, 96% were accepted.
Chisholm (2000) USA	61 TP NM	Prospective uncontrolled Ambulatory	To assess drug cost savings resulting from a clinical pharmacist-managed medication assistance program for renal transplant patients designed to assists patients to procure immunosuppressant from	12	-Patients who were unable to purchase their immunosuppressant were enrolled in manufacturer's medication assistance programs.		-For each dollar spent in pharmacist's time, a minimum of \$4 was returned to the institution.

pharmaceutical manufacturers.									
Gonyeau (2005) USA	292 CKD 79 (NM)	Prospective uncontrolled Inpatients	Assessment of impact and acceptance of pharmacy interventions on appropriate dosing	6 week	-Dose monitoring and adjustment	-Dosing appropriateness -PhR acceptance rate -Prevention of ADR and errors -Cost savings	-15% increase in appropriate renal drug dosing (66.5% to 81.2% P<0.0001), -38% of interventions accepted. -5 ADR and 3 medication errors prevented -Cost savings of \$29,166		
Moretti (2006) USA	242 CKD NM	Randomised controlled Ambulatory	Determination of the impact of ambulatory clinic pharmacist on EPO treatment goals	2	-Recommendations on <ul style="list-style-type: none">• Obtaining more recent labs tests• Need for iron supplementation -Dose monitoring and adjustment (EPO)	-PhR acceptance rate	-75% of PhR were accepted.		
Nichols (2001) USA	NM dialysis NM	Prospective uncontrolled Inpatients	Assessment of pharmacy based EPO dose management protocol for a dialysis unit	8	-Dose monitoring and adjustment <ul style="list-style-type: none">• EPO dose determined by monthly HCT level	-HCT level -Cost savings	-Improved HCT level after intervention (24% of patients had HCT<30 in baseline VS. 5% of patients had HCT<30 in endline) -Drug cost savings of \$374,000 annually (Drug cost reduced		

					<ul style="list-style-type: none">Syringes prepared in pharmacy from multi-dose vials	from \$50 per patient per treatment to \$30)	
Pardo (2002) Spain	215 CKD NM	Prospective uncontrolled Inpatients	Assessment of impact of pharmaceutical interventions on elderly patients with a low creatinine clearance	3	-Dose monitoring and adjustment	-Cost saving	-Saving of \$384.53 over a three-month period.
Tanprayoon (2009) USA	80/80 CKD 66.7 (13.4) 65.4 (15.6)	Prospective historical control Inpatients	Evaluation of the impact of a pharmacist-driven EPO monitoring program		-Dose monitoring and adjustment (appropriateness of EPO dose regimen -Need for adjuvant iron therapy assessed	-Correct indication -Correct dosage regimen	-Intervention group compared to control had more appropriateness in <ul style="list-style-type: none">Indications (64 vs. 70 patients)Dosing regimen in intervention than control group (65 vs. 70 patients)Iron replacement and laboratory studies (61 vs. 76 patients) -35 out of the 60 interventions were accepted.

Grabe (1997) USA	45 HD 52(16)	Retrospective uncontrolled Ambulatory	Evaluation of DRPs and impact of clinical pharmacist interventions in HD patients	1	-Medication review -Drug monitoring and adjustment -Therapeutic recommendations	-PhR acceptance rate	-81% PhR accepted. -6.9% PhR had no significance -78% PhR were significant -4.9% PhR were very significant -1% were extremely significant
Ohnishi (2011) Japan	84 HD NM	Retrospective uncontrolled Ambulatory	Assessment of pharmacist-implemented management program to ensure appropriate use of erythropoietin-stimulating agents	12	-Drug monitoring and adjustment -Therapeutic recommendations (changes in the dose of erythropoietin and administration of iron preparations)	-Hb level	-Optimal Hb levels achieved in patients with low Hb level (<10 g/dl). -Reduction in Hb level in patients with higher Hb level(>12 g/dl)
Tang (1993) USA	50 HD NM	Retrospective uncontrolled Ambulatory	Assessment of role of a clinical pharmacist in care of patients receiving chronic HD	6 week	-Therapeutic recommendation on drug selection, drug discontinuation, dose selection, therapeutic monitoring	-Positive outcomes	-90.5% intervention resulted in positive patient outcome -7.9% intervention resulted in no observable change or had no effect on outcome -1.5% interventions showed negative outcomes

Pai (2009) USA	107 HD (46/61) 55.8 (15.1) 60 (15)	Randomized controlled Ambulatory	Evaluation of the effect of pharmaceutical care on HRQOL in HD patients.	2	Medication review	-RQLP questionnaire	HRQOL did not worsen in pharmacist intervention group and it was maintained as such for an additional year.
Soler (1996) Spain	22 HD (BL) 29 HD (1991) 38 HD (1994) 40 HD (1995) NM	Prospective Uncontrolled Ambulatory	Evaluation of clinical and economic benefits of collaboration between hospital pharmacy services and dialysis centre to control the use of epoetin	48	Implementation of a standard protocol for dispensing and utilisation of epoetin	-HCT level -Hb level	-Elevation in HCT, Hb and ferritin level -Reduction in levels of iron and transferrin saturation.
Alvarez (2009) Spain	185 (88/97) CKD, drugs with renal risk	Prospective uncontrolled Inpatients	Comparison of adherence of prescriptions according to the dosage guide before and after applying pharmacist intervention programme	2	-Drug monitoring and adjustment	-Adherence -Cost saving	-Reduction in non-adherence after intervention (18.7% vs 2.1%) -Significant cost saving due to intervention
Golightly (1993) USA	627 CKD NR	Retrospective Uncontrolled Inpatients	Assessment of effectiveness of a program for monitoring drug prescriptions in renal patients		-Medication reviews -Drug monitoring and adjustment -Assessment of creatinine function -Recommendation to physician	-Change in drug therapy	-233 changes in drug therapy

Patel (2005) USA	119 CKD	Prospective uncontrolled Ambulatory	Evaluate opportunities for pharmacists to work collaboratively with physicians to improve medication use and CKD patient outcomes.	NM	-Review of medical records, -evaluations of DRPs, -therapeutic recommendations	-PhR acceptance	-40.9% of the recommendations were accepted.
Possidente (1999) USA	31 HD, 6 PD	Retrospective uncontrolled Inpatients	To evaluate the continuity of drug therapy and the incidence of drug-related problems (DRPs) in long-term dialysis patients who required hospitalization	14 weeks	-Medication review -DRPs identified -Recommendation to physician	-PhR acceptance	-Physicians accepted 154 of the 161 recommendations. -Clinical significance of the accepted recommendations was: somewhat significant, 24.7%; significant, 58.4%; very significant, 16.9%.
Chertow (2001) USA	17,828 CKD (7887/9941) 52.5 (18.4) 52.5 (18.3)	Prospective randomised controlled Inpatients	Determining the effect of a system application (merged with COE) for adjusting dose in patients with renal insufficiency in drug prescribing and patient outcomes.	8	-CDSS(default dose, frequency, recommendations displayed to the order-entry user)	Rates of appropriate prescription -Hospital and pharmacy costs	-Dose appropriateness was 67% in test vs. 54% in control -Mean length of hospital stay was 4.3 (4.5) days in test vs. 4.5 (4.8) in control -No significant differences in estimated hospital and pharmacy costs.
Nash (2005) USA	NM CKD NM	Prospective uncontrolled Inpatients	Determining the impact of MSRS in addition CPOE to by detecting the	NM	MSRS (dose recommendation based on renal function)	-Rate of over dosing	-Decreased rate of over dosing of medications requiring adjustment

			administration of excessive doses of medication in patients with CKD			-Proportion of medication errors	23.2% to 16.8%
Bhardwaja (2011) USA	32,917 (3025/3100) CKD	Randomized controlled Community	To determine whether a computerized DRAP program could decrease the rate of medication errors in drug selection or dosing in patients with renal insufficiency	15	-DRAP (alert pharmacists at the time of dispensing to possible errors in drug selection and dosing)	-Proportion of medication errors	- Proportion of medication errors was significantly lower in the intervention group than the control (33% vs 49%, P<0.001).
Weinhandl (2013) USA Find full text	51877 (43,013 /8,864) HD NM	Prospective Controlled Ambulatory	To determine outcomes of integrated pharmacy program for haemodialysis patients		-Medication review -telephonic medication therapy management,	-Rates of death and hospitalization.	-Lower rates of death and hospitalization
Wang (2008) Taiwan	37 transplant NM	Prospective uncontrolled Inpatients	To investigate effects of clinical pharmacist joining transplant clinic to provide pharmaceutical care on treatment outcomes	15	-Medication review -Therapeutic recommendations	PhR acceptance rate	-More than ninety percentages of PhR were accepted -94.2% of the patients showed improved disease conditions in which the PhR was accepted.
Via-Sosa (2013) Spain	350 (176/174) CKD 83.1(7.21)	Prospective controlled Community	To evaluate the effectiveness of the community pharmacist's intervention in improving dosing	7	-Dosing review for drugs requiring adjustment -Recommendation to the physician	-Prevalence of DRPs	-Difference in the dosing inadequacy and mean drug-related problems between the

inadequacy in elderly patients				control and intervention group was increased after the intervention. (P < 0.001)			
Barnes (2014) USA	146 CKD 71.6 (12.2)	Prospective Uncontrolled Ambulatory	To evaluate pharmacist-driven renal medication dosing intervention	12	-Medication review -ensure all medications are prescribed correctly based on renal function -Provide recommendation to physician	-Rate of use of aspirin, ACE-Is/ARBs -PhR acceptance rate	-Use of ACE-Is/ARBs and aspirin increased to 77% and 82% from 73% and 72% respectively. - 65.2% recommendations were accepted by the physicians.
Ribed (2013) Spain	449 CKD NM	Prospective uncontrolled Inpatient	To evaluate a program implementing a dose adjustment alert system according to the patient's renal function.	2	-Dosing and adjustment --Provide recommendation to physician	-Rate of use of aspirin, ACE-Is/ARBs -PhR acceptance rate	- Recommendation acceptance rate of 70%.
Joost (2014) Germany	67 (35/32) TP 54 (11.9) 51 (13.3)	Prospective controlled Inpatient	To investigate the impact of a pharmaceutical care programme on daily drug adherence during the first year after renal transplantation.	24	-Medication review -counselling sessions (immunosuppressive drug therapy the mechanisms of transplant rejection, drug actions and dosing drug-drug interaction	-Drug adherence -Changes in HRQoL	-Drug adherence improved significantly after the intervention (P = 0.014)

					adverse effects written information material. adherence support,		
Jiang (2013) China	NM CKD	Prospective uncontrolled Inpatients	To evaluate the effects of dosing adjustments performed by pharmacists on the length of intensive care unit (ICU) stay, ICU cost, and antimicrobial adverse drug events (ADEs).		-Drug dosing and adjustments	-Length of intensive care unit (ICU) stay, -ICU cost -Antimicrobial adverse drug events (ADEs)	-Reduced length of ICU stay from 10.7 +/- 11.1 days to 7.7 +/- 8.3 days (p = 0.037) -Cost savings of \$3525 per septic patient -Decrease in ADE (P = 0.048).
Jiang (2014) China	103/106 Dialysis 61.3 (16.9) 58.9 (17.3)	Prospective uncontrolled Inpatient	To examine the effectiveness of pharmacist dosing adjustment for critically ill patients receiving continuous renal replacement therapy (CRRT)	12	-Dosage adjustment	-PhR acceptance rate cost savings	-90.98% of the recommendations were accepted by the physicians -Cost saving of US\$2,345.98 cost savings per critically ill patient receiving CRRT -Decline in adverse drug events (P<0.001).
Gracia (2013) Spain No full text	47 CKD 79.2 (7.9)	Prospective uncontrolled Inpatient	Evaluate the outcomes of a pharmacist intervention for drug dosage adjustment of renal risk in patients with chronic kidney disease	7	-Medication review Therapeutic recommendation	-PhR acceptance	81.5 % of interventions were accepted

(CKD) during their admission in a short stay unit (SSU).							
Diaz (2013) Spain	171 CKD 76.4	Prospective uncontrolled Inpatient	-Implementation of a computer-based, semi-automated system to optimise the drug prescribing in patients with renal impairment	3	-A system for drug dosage adjustment integrated into the Hospital computer provider order entry system.	-Frequency of appropriate prescription and accepted recommendatio ns	-Increase in appropriate prescribing from 65% to 86% after intervention. (P=0.001). -60% of the recommendations were accepted.
Borolossy (2014) Germany	50 (25/25) HD 11.5 (0.6) 10.8 (0.64)	Prospective Randomised controlled Ambulatory	To evaluate the impact of interventions by the clinical pharmacist on the clinical outcome of children undergoing haemodialysis	9	-Medication review -Start or discontinue a drug; increase or decrease a dose; -Patient education (disease, drug therapy) -Promote patients' adherence	-Serum levels of calcium (Ca), phosphorus (P), parathyroid hormone -Health-related quality of life	Test group in comparison to controlled group showed a significant decline in -Systolic and diastolic blood pressure (P=0.0001), -Serum phosphorus level (P=0.006) and -Parathyroid hormone level (P=0.001) -Serum Ca*P product level of the test group (P=0.001) -Satisfaction with the renal treatment significantly

											improved in the test group (P=0.0001)	
Cabello-Muriel (2014) Spain	249 (124/125)	Prospective controlled Inpatient	-To evaluate the effectiveness of a pharmacist-physician intervention program in managing patients with CKD	6	-Medication review -Inform the physician about potentially nephrotoxic drugs -Alert the physician about the drugs requiring dosage adjustment -Propose a recommended dose adjustment.	-GFR on admission and at discharge	-Intervention lowered the percentage of potentially nephrotoxic drugs unadjusted to renal function from 26.7% (88 of 329) to 6.9% (23 of 329). -Clinical impact of this improvement could not be analysed due to shorter study period.					
PD: Peritoneal dialysis PhR: Pharmacist recommendations, HC: Historical control, CrCl: Creatinine clearance, HRQOL: Health related quality of life, ADR: Adverse drug reactions, TRPs: Treatment related problems, RQLP: renal quality of life profile, P:Phosphate, Ca P:Calcium-phosphate, MTM: Medication therapy management, CDSS: Computerised decision Support System, COE : Computerized order entry , DRAP: Drug renal alert pharmacy, MSRS: Medication safety reporting system, MPE: Medication prescribing error, ACE-Is: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers												

Table 8.2 Intervention focused on optimising drug therapy in CKD

Pharmacist intervention- Educational activities

The most common educational intervention was providing verbal instructions to patients, which included counselling regarding disease, drugs, and lifestyle modifications, use of medication, management of complications and comorbidities and the importance of regular dialysis.^{150 244 329-332} Written educational materials or books were given to patients on request.³²⁹
³³¹ Pharmacists provided unstructured counselling, lasting for fifteen minutes on each alternating visits and this was successful in improving health related quality of life for haemodialysis patients. Quality of life was determined by the generic instrument World Health Organisation quality of life questionnaire which comprised of 26 items, that measures four domains: physical, psychological, social and environmental. Clinical pharmacists provided counselling, solely focused on medication, and this lead to significant improvement in patients' medication knowledge and adherence.³²⁹ A cross over randomised trial³³² conducted to evaluate the impact of educational interventions on medication knowledge in haemodialysis patients reported an increase in the knowledge level of patients after intervention. The pharmacist intervention comprised of a structured face-to-face interview session of 25-30 minutes to assess the medication knowledge of the enrolled patients followed by appropriate counselling. The test group showed significant improvement in medication knowledge at week sixteen of the study. Chisholm et al³³³ addressed the impact of a clinical pharmacist service on transplant patients in terms of adherence with immunosuppressant agents. Adherence enhancement strategies were implemented in the intervention group where a pharmacist counselled patients regarding the drug therapy and the correct method for taking medications. The control group was exposed to routine clinical services only. Adherence rate in the intervention group was statistically higher than for the control group ($p < 0.001$). Further, the test group had a longer duration of adherence than the patients in the control group ($p < 0.05$)

Reference Author Year Country	Patient characteristics N(C/T) Age (Years) Mean (SD)	Study design/ Settings	Aim	Duration (months)	Intervention	Key measurement	Result
Thomas (2009) India	56 (28/28) HD 47.5 50.2	Non- Randomised controlled Ambulatory	To assess the impact of patient counselling on HRQOL of HD patients	6	-Patient education and training on diet , life style modification, medication and disease	HRQOL	Health related quality of life in test group showed a consistent improvement of 2% in six months
Sathvik (2007) India	90 (45/45) HD 50.69 (13.69) 47.29 (17.78)	Crossover randomised Inpatients	Evaluation of impact of pharmacist educational program on medication knowledge of the patients	4	-Patient education and training	MKAQ	Improvement in MKAQ scores after intervention
Chisholm (2001) USA	24 (12/12) TP 49.2 (10.2)	Randomised controlled Ambulatory	Assessment of impact of clinical pharmacy services on renal TP patients' adherence with immunosuppressive medications	24	-Patient education and training -Drug therapy monitoring -Medication review	Adherence rate	Intervention group had higher mean CR, longer duration of adherence, faster achievement of target level of adherence
Abraham (2012) India	81 (46/35) HD 48.2 (12.6) 50.7 (12.1)	Prospective controlled Ambulatory	Estimation of effect of patient counselling in quality of life of ESRD patients	12	-Patient counselling on disease, diet, exercise, lifestyle modification, use of medication and the	World Health Organisation Quality of life scale	-Improvement in physical psychological, environment and social domain (P<0.001) -Improvement in quality of life

					importance of regular dialysis		-Delayed progression of renal failure
					-Verbal and written materials provided		
Aburuz (2013) Jordan	130 CKD 56.3 (17.8)	Prospective uncontrolled Inpatients	To implement and evaluate the impact of pharmaceutical care service for hospitalised patients with CKD	3	-Patient education on diet, smoking cessation and management of comorbidities and complications -Provide recommendation to physician	-Nature and prevalence of TRPs -Clinical significance of TRPs -PhR acceptance rate	-86% PhR accepted -17% TRPs resolved -5.5 % TRPs improved -37.4 % TRPs prevented -Better management of comorbidities
Bayliss 2011 USA	1769/233 CKD 68.29 (12.29) 67.62 (11.28)	Historical control Community	To determine if multidisciplinary team (MDT) care slows the rate of decline in renal function	4 yrs	-Patient education on disease, medication, management of comorbidity and complications, diet. -Medication reconciliation -Nephrology consultation including medical recommendations for comorbidities and complications	-Decline in GFR level -Values of LDL, HbA1c, and BP	-Decline in mean GFR value in usual vs MDT group: 1.2 mL/min vs 2.5 mL/min (P< 0.0001) -Fewer chronic conditions in MDT patients -No differences in the BP, HbA1c, or LDL value.

Bertsche (2009)	68 CKD 65.3 (13.8)	Prospective Uncontrolled Inpatient	To assess the effect of drug information counselling for clinicians on the appropriateness in drugs requiring dose adjustment in intensive-care patients	3	-Calculate renal function -Determine the appropriate dose based on renal function -Provide recommendation to physician whenever drug adjustment is required	-Prevalence of overdosed drugs before and after the intervention	-Extent of overdose was reduced from 54% before to 31% after the intervention (P<0. 001).
Rani (2013)	85 HD 50.52 (13.28)	Prospective uncontrolled Ambulatory	To assess the effect of patient counselling in improving their medication knowledge and adherence	3	-Patient counselling (disease, dialysis procedure, the drugs, diet and fluid restrictions) -Information leaflets	-MKAQ (Medication knowledge assessment questionnaire) score -Brief Medication questionnaire (BMQ)	-Significant increase in the medication knowledge from baseline (P= 0.000). -Significant increase in mean BMQ score indicating improved adherence (P=0.000).
HD: Haemodialysis, HRQOL : Health related quality of life, MKAQ : Medication Knowledge Assessment Questionnaires, CP: Adherence rate, TP: Transplant patients, ESDR: End Stage Renal Disease							

Table 8.3 Intervention focused on patient education and training

8.4.3 Outcomes of pharmacist intervention

The outcomes that can be most influenced by pharmacists' interventions are the clinical/physiological, humanistic, drug-related and economic outcomes.

Clinical/physiological outcomes

The protocol driven administration of erythropoietin managed by pharmacists resulted in a faster achievement of target haemoglobin level with use of lesser dose of erythropoietin.³¹² Implementation of an anaemia management protocol along with epoetin and iron therapy dose monitoring/ adjustment resulted in significant elevation in haemoglobin and transferrin saturation value and an increase in the number of patients with target haemoglobin level.^{214 295 299 303 307 311-314} A pharmacist-run anaemia education program providing medical therapeutic information to the patients along with information on using an administration device for self-injection of epoetin resulted in improved patient adherence with an optimal haemoglobin level within two months.³⁰⁹ Similarly, pharmacist-provided patient education and training on medication along with implementation of serum phosphate management protocol lead to reduction in serum phosphate level.²¹⁰ Drug use evaluation, providing drug information and therapeutic recommendations to the physician on renal anaemia in ESRD resulted in an increased trend of mean haematocrit in patients.³¹⁰ Dose monitoring and adjustment for darbopoietin resulted in an increase in the number of patients exhibiting a haemoglobin target range.^{225 304} Conversion of erythropoietin administration from the intravenous to the subcutaneous route lead to improvement in the level of haematocrit.²⁹² Preparation of IV calcitriol by the pharmacist for each patient on a daily basis led to a significant decrease in the number of patients with moderate to severe hyperparathyroidism.³¹⁹ Clinical pharmacy services that included a pharmacist performing medication reviews with an emphasis on preventing or resolving medication-related problems and implementing adherence-enhancing activities, produced a significant decrease in systolic and diastolic blood pressure, along with an increase in the number of patients reaching target levels for blood pressure.^{317 318}

Pharmaceutical care services, which included ongoing medication review and providing appropriate pharmacotherapy recommendations, reinforcing patient adherence, and suggesting use of renin-angiotensin system inhibitors, had a positive impact on patients' blood glucose control along with an increase in the number of patients at target goals for blood pressure, glycosylated haemoglobin and cholesterol levels.^{301 316} The dyslipidaemia control

program consisting of ordering/assessment of lab tests, dose optimisation and providing recommendation to physicians resulted in reduction in total cholesterol level [mean (SD) 80(3) vs 96(5) mg/dl] along with increase in patients reaching target levels for low density lipoprotein.^{294 315}

Comprehensive clinical pharmacy services that included dose monitoring and adjustment, education and training on disease and medications, drug use evaluation to manage the multiple complications in haemodialysis patients also resulted in optimal serum calcium, parathyroid hormone, haemoglobin, cholesterol level etc.^{305 321 322} and delayed progression of renal failure.³³⁴ Pharmacist intervention comprising of medication review and drug dose adjustment was effective in reducing the duration and rate of all causes for hospitalisation.^{220 335}

An integrated pharmacy program for haemodialysis patients that included telephonic medication therapy management was associated with lower rates of death and hospitalization.³²⁷ There were fewer all cause hospitalisations [1.8(2.4) vs. 3.1(3.0)] and shorter hospitalized times (9.7 +/- 1.4.7 vs. 15.5 +/- 16.3 days) in the pharmaceutical care group compared with the standard care group in a randomised controlled study.²²⁰ The effort of pharmacists in optimising the dose for haemodialysis and transplant patients led to a significant reduction in occurrence of ADR and medication errors.^{119 300}

Humanistic outcomes

Pharmacists conducted counselling on diet, life style modification, medication and disease for haemodialysis patients resulted in improvement in health related quality of life measured using the World Health Organisation Quality of life scale.³³⁴ Pharmacist mediated medication review and therapeutic recommendation lead to an increase in quality of life.²¹⁹

Implementation of adherence enhancement strategies like counselling transplant patients regarding drug therapy and the proper ways to take medication resulted in improvement in adherence rate.³³³ Furthermore, pharmacist dose monitoring and adjustment showed reduction in non-adherence. Counselling sessions focusing on immunosuppressive drugs, the mechanisms of transplant rejection, drug actions and dosing drug–drug interaction adverse effects and providing written information material and adherence support lead to an increase in adherence with medications.¹⁶⁵ Similarly, in a study with a historical control group,

there was reduction in physician's non-adherence with dosing guidelines by 27.5% after the pharmacists started monitoring patients drug therapy.¹¹⁹ Educational interventions comprising of a structured face-to-face interview session of 25-30 minutes to assess the medication knowledge of enrolled patients followed by appropriate counselling resulted in an increase in the knowledge level of patients.³³²

Pharmacists provided therapeutic recommendations to the physicians in more than 50% of the trials. However, none of the studies had the complete (100%) acceptance of the recommendations. More than 90% of the therapeutic recommendations provided by the pharmacist were accepted by the physicians in eight studies.^{151 152 306 324 336 337} Nine studies had acceptance between 50-90%.^{119 293 298 323 328 338-341} Two studies had an acceptance rate of less than 50%.^{227 300} Physician acceptance of pharmacist recommendations resulted in changes to therapy in two studies.^{152 342} Few studies classified the impact of recommendations as- 'non-significant, significant, very significant and extremely significant' and greater than 50% of the recommendations were significant in all studies.^{151 324 341} In the patients group in which the physician accepted the pharmacist's recommendations, patients showed improved disease conditions.^{324 337}

Drug-related outcomes

The renal dosing service provided by the pharmacists led to an increase in appropriate dosing and a reduction in physician's nonadherence with dosing guidelines and drug-related problems.^{119 293 300 342 343} In a prospective uncontrolled study with hospitalised patients with CKD, there was a 15% increase in appropriate renal drug dosing from 66.5% to 81.2% after pharmacist intervention.³⁰⁰ Dosing adjustments performed by pharmacists in critically ill patients lead to a decrease in adverse drug events.^{335 336} Use of decision support systems for adjusting the dose in patients with renal insufficiency resulted in an increase in dose appropriateness and a decreased rate of overdosing.^{135 308 326 340} The average weekly dose of erythropoietin was reduced after the route of administration was changed from intravenous to subcutaneous.²⁹² Further, there was improvement in dosing of erythropoietin and iron.

Economic outcomes

The implementation of pharmaceutical care programs for patients with CKD resulted in positive economic outcomes. A clinical pharmacist-managed medication assistance program in a renal transplant clinic produced substantial cost savings over this one-year study period. For each dollar spent in the pharmacist's time, a minimum of US \$4 was returned to the institution.³⁴⁴ The drug cost reduced from US \$50 per patients per treatment to US \$30 after the pharmacists were involved in determining the erythropoietin based on monthly haematocrit levels.²⁹⁷ Pardo et al showed the savings of US \$384.5 over a three-month period after pharmacists started monitoring the drug dose for elderly patients with renal impairment.²⁹⁶ Cost savings of US \$2250 was observed within 8 months of implementation of dose adjustment programs in a prospective observational study.¹¹⁹ Similarly, there was cost savings of US \$29,166 after a 6 week of implementation of a dose monitoring program for hospitalised patients with CKD.³⁰⁰ Drug dosing adjustments performed by pharmacists for intensive care unit patients lead to cost savings of US \$3525 per septic patients.³³⁵ Drug dosing adjustments performed by pharmacists for critically ill patients receiving continuous renal replacement therapy resulted in cost savings of US \$2345.98.³³⁶ The implementation of a erythropoietin management protocol led to reduction in erythropoietin dose per treatment, resulting in significant cost avoidance annually.³⁰⁷

8.5 Discussion

Overall, the pharmacist interventions appeared to have a positive effect on patient outcomes concerning physiological and biochemical parameters (blood glucose, lipid level, blood pressure, haemoglobin level etc.), incidence of adverse drug reactions, knowledge, satisfaction, adherence, quality of life in patients and the occurrence of drug-related problems. Most importantly, the pharmacist medication review appeared promising in decreasing the rate of over dosing of medications requiring adjustment. Drug use evaluation and monitoring was successful in reducing the usage of unnecessary drugs and improving physician adherence to dosing guidelines. Pharmacists management of comorbidities generally, but not always, had better outcomes in comparison to physician's management. A total of 14 trials included data on the burden of costs to patients, none of which performed formal economic evaluations. All of the studies conducted a simple cost analysis, targeting the prescribing costs and yielded a significantly positive outcome.

Methodological Critique

The primary concern regarding the methodology of the included studies would be the study design. The majority of the studies included in the analysis had an uncontrolled design. An uncontrolled design determines the relationship between the variables in the study but it restricts developing the casual relationship in general.³⁴⁵ The impact of pharmacist intervention can be measured only with the randomised controlled trials that reports clear descriptions of patient's demographics and the intervention preformed. The lesser amount of randomised controlled trials performed creates limitations to the quantification of the results. Significant comparison could not be performed due to the diversity of the tools utilised in the studies. The average sample size in the studies was small therefore, the generalisation of the results to the greater population would not be convenient. The included studies lack full details regarding sample recruitment. Some studies did not report the sample size and one of the reasons for this might be attributed to the inclusion of the congress abstract in our reviews. Some studies lacked the date of data entry follow up time. It is recommended that outcomes that are clinically significant should be presented clearly and it is desired that the outcomes presentation be consistent with the economic, clinical, humanistic (ECHO) outcomes model to provide clear insight concerning the results.³⁴⁶ However, very few studies have followed this method.

Two studies assessed medication knowledge of hemodialysis patients using a Medication Knowledge Assssment Questionnaire. In the first study, the administered questionnaire was developed and validated by the investigators³³² and the second study used the validated questionnaire from the first study.³²⁹ The content validity of the questionnaire was performed through a literature review, discussion among a panel of experts (nephrologist and clinical pharmacist), and a focus group discussion amongst patients. The questionnaire was pilot tested using a convenience sample of hemodialysis patients to assess reliability.

Most of the interventions were carried out in hospital settings. Very few studies identified addressed patients with CKD in the community. Studies focusing on educational interventions identified by our search terms were conducted in haemodialysis patients. None of the studies tested patients with early stages of CKD. In fact, educational intervention is equally important for patients in this stage in order to prevent progression of CKD. Another weakness of the studies was that there was no clear definition of 'usual care patients' in the control groups. Most studies did not have a control group for comparison and there was no

baseline assessment of adherence which made it difficult to evaluate the effect of interventions. We could not perform a meta-analysis due to the heterogeneity of the studies. Quality control report of the literature review could not be presented, as the literature search and screening of the articles according to the inclusion criteria was carried out solely by the candidate.

Findings in comparison with other studies

The findings from this review are consistent with the results of similar studies.³⁴⁷⁻³⁴⁹ However, the findings from our study are reinforced by the use of multiple databases, strict inclusion criteria and a comprehensive search strategy. Our search terms covered various descriptive studies that did not report the outcomes of intervention rather they reported the intervention process. We excluded such studies with the rationale that we cannot expect the intervention to always create positive results.³⁵⁰

Conclusions and recommendations

-Studies included in the review demonstrate that DRPs are very frequent and are increasing in patients with renal insufficiency. The most common DRPs found in the included studies were incorrect dose, adverse drug reactions, and inappropriate drug therapy. Cardiovascular drugs and anti-infective agents were the most common classes of medications causing DRPs. The decrease in DRPs frequency after pharmacist involvement reflects the need for the pharmacist to be involved in the treatment of CKD. Further, the high level of acceptance of pharmacists' recommendations by physicians indicates the greater need for pharmacists to be involved in the care of renal insufficiency.

-The included studies demonstrated that the pharmaceutical care implementation is related to tangible benefits on clinical, humanistic, economic and, drug-related outcomes in various stages of CKD, dialysis, transplant patients in different settings; ambulatory, transplant clinic, dialysis unit, community and hospital wards. Therefore, incorporation of pharmacist in the care of chronic kidney disease patients should be considered in health care policy decisions.

-Patients with CKD, especially dialysis patients, have a very high economic burden related to the direct (hospital and drug cost) and indirect cost of treatment (abstinence from work) etc. The findings from the reviewed studies, demonstrates that providing pharmaceutical

care is a successful means for avoiding the costs associated with drug therapy, hospitalisation and DRPs etc.

-CKD is believed to degrade the quality of life in patients. However, the awareness of the patients regarding diet and medication through counselling proved to be an effective means for increasing their quality of life. The counselling by pharmacists was more effective in improving the psychological domain and removing misconceptions about CKD.

-The studies confirm that there is poor medication knowledge (name, indication and dosage regimen) on the part of the patients with CKD. The education provided by the clinical pharmacists resulted in considerable improvement to patient's knowledge. There seems to be a need for the continued education of the patients so that they better understand the disease and the associated medications. A trained pharmacist could play a vital role in educating CKD/haemodialysis/transplant patients, which has obvious benefits for therapeutic outcomes.

-Longer duration studies are required to evaluate the continuous clinical pharmacy activities. Appropriate care for patients with CKD must occur in the earliest stages, preferably before progression to more severe stages. Patients who received clinical pharmacy services in addition to routine clinical services had better adherence to treatment than patients who only received routine clinical services. The results of these trials suggests the need for a multidisciplinary team that includes a clinical pharmacist as a part of the care of patients with CKD. This is beneficial for achieving the desired therapeutic outcomes in patients with CKD.

-This review supports the idea of incorporating a clinical pharmacist to improve therapeutic effectiveness, quality and safety of patient care. Implementing clinical pharmacy services for the care of patients with CKD can be tedious and difficult if the institution requires the provision of new resources. However, the advantage of pharmaceutical interventions as reported in the studies in this review is that most clinical pharmacy services leads to positive economic outcomes - a net hospital cost benefits/patients cost burden in terms of cost avoidance, reduced use and occurrence of ADRs.

-However, more research is needed to better understand the role of the pharmacist in the community settings especially for the elderly with deteriorating renal function. Lastly, there is a need for multicentre, randomised controlled trials of a longer duration in larger populations to determine the benefits to the health care system for incorporating pharmaceutical care programs for patients with CKD.

-Most of the interventional studies are conducted in the USA and not a single interventional study was conducted in Australia. It would appear that there is a need for interventional studies in Australian settings.

Chapter 9 OVERALL DISCUSSION, FUTURE DIRECTIONS AND CONCLUSION

CKD management guidelines are regularly disseminated by nephrology professional bodies and are designed to reduce the occurrence and progression of CKD, and to improve the quality of care. Despite the readily available evidence-based guidelines and standard drug information sources, there is suboptimal prescribing in patients with CKD. The need for dose adjustment in renal impairment often goes under-recognised, potentially leaving patients exposed to a higher risk of adverse drug effects. The five studies outlined in this thesis were conducted to quantify the extent of this problem in the Australian setting, to explore the factors that influence them and to recommend the areas that need intervention to improve the usage of high-risk medications in patients with CKD.

The analysis of medication review cases revealed that both aged-care residents and community-dwelling older people are often prescribed renally-cleared medicines, outside of the recommended guidelines. Drugs like perindopril, fenofibrate, olmesartan, gliptins, metformin, bisphosphonates, strontium and ACE-inhibitors were the most inappropriately prescribed medications. Patients in aged-care were more likely to be prescribed medication inappropriately. Older age, and the presence of diabetes and heart failure were found to be associated with patients being prescribed medications inappropriately.

There was a lack of renal dosing information in the standard information sources. Additionally, there was poor consistency in dosing recommendations and renal function severity terms used among the sources. This can adversely affect prescribing practices as it may confuse or mislead the prescriber and potentially cause them to refrain from using these information sources.

Regular updating of the drug information sources is warranted, along with a need for all drugs that are to be used in patients with renal dysfunction to undergo at least one pharmacokinetic study in patients with varying degrees of renal impairment prior to marketing. An expiry date should be assigned for PIs in order to enforce upgrading the information with time. Uniformity in the categorisation of renal impairment and renal dosing information would be beneficial to reduce the possibility of inappropriate dosing.

The marked discrepancies in doses rendered using various renal function estimating equations complicate the prescribing decision. There is need for a long-term multi-centre study in a diverse population to define the clinical effects of the discrepancies among the equations

for drug dosing. Use of a single kidney function estimate for detection, drug dosing and management of CKD would facilitate better health care delivery. It can potentially address the confusion associated with the existing practice of using different formulae for different purposes.

Pharmacist-conducted drug usage evaluation and monitoring appeared promising in decreasing the rate of over dosing, usage of unnecessary drugs, and improving physician adherence to dosing guidelines. The problem of dose inappropriateness could be addressed to some extent, by provision of HMRs and RMMRs as these have been found to be effective in reducing the use of potentially inappropriate medicine for elderly people in the community. The high level of acceptance of pharmacists' recommendations by the physician indicates the greater need for pharmacists to be involved in the care of patients with CKD. Therefore, incorporation of the pharmacist in the care of patients with CKD should be considered in health care policy decisions.

The GPs included in our study expressed relatively low awareness of CKD management guidelines, uncertainty around acceptable renal function tests, confusion surrounding the most correct test for renal dosing and a desire for intervention programs to improve CKD care. Additionally, the GPs expressed concerns over the inadequate and ambiguous renal dosing recommendations included in the drug information sources. Time constraints, risk of over-diagnosis associated with automated eGFR, practitioner's inertia and the logistics of getting a test before prescribing, were some of the challenges to ordering a kidney function test.

Addressing these barriers to using the guidelines with concrete interventions at the levels at which they occur would help to improve the dosing in patients with CKD. A series of brief, individualised training sessions on available sources and updated information on renal dosing could help enhance skills to effectively access information sources. Designing and implementing a tool that integrates multiple information sources into a single interface, would decrease the time required to seek information and help prescribers consult multiple sources, each with a varying design and interface in a single platform. Decision support systems can be incorporated within the prescribing software, that could alert the provider to potentially order a renal function test. The alert could also provide references to guidelines and information sources that would guide dosage adjustment. Online medical education focusing on updated information can potentially address the confusion associated with the existing practice of using different formulae.

Guidelines that are unclear, controversial or based on opinion are less likely to be employed in clinical practice. Updating the information sources to present the key elements in an unambiguous format, in conjunction with efforts to build consensus among the standard information sources, may be necessary. GPs can accordingly incorporate the recommendations into practice.

In conclusion, improved dissemination of existing guidelines, online education to increase awareness of available guidelines, and decision support systems to aid GPs in identifying renally-cleared drugs appear warranted. Formulating education and training programs for general practitioners and pharmacists geared towards recognising drugs that require caution in renal impairment and the patients at risk is required. Integrating non-dispensing pharmacists within general practices could support the delivery of healthcare services and improve patient outcomes. Non-dispensing pharmacists in general practice can assist GPs in a range of areas such as medication management, and developing and managing drug safety monitoring systems. Particularly in CKD management, pharmacists can support GPs in prescribing by offering advice on renally cleared drugs, drugs to be avoided or used with caution in renal impairment and recommending alternate treatment options. Pharmacists co-located in general practice can design and deliver patient education sessions to facilitate increased medication adherence. Accredited pharmacists conducting HMR and RMMR services, contribute to reducing medication errors and adverse drug events and ensure the safe and effective use of medicines. These services assist GPs in making better judgments concerning patients who require additional medication monitoring and can reassure GPs that patients are being managed appropriately. Studies are needed to understand if such interventions could improve prescribing practices without substantial economic impacts or disrupting the general practice workflow.

Appendix 1. List of renally-cleared Drugs examined in the study

Drugs/Usual maximum dose	Dosage adjustment in relation to CrCl values	
	Creatinine Clearance, mL/min	Maximum dosing recommendation, mg
Metformin 500-3000 mg daily	60–90	2000 daily
	30–60	1000 daily
	<30	Avoid use
Glibenclamide 2.5–20 mg daily	≤50	Avoid use
Saxagliptin 5 mg once daily	<50	2.5 once daily
Sitagliptin 100 mg once daily	30–50	50 once daily
	<30	25 once daily
Vildagliptin 50 mg twice daily	<50	50 once daily
Perindopril <i>Perindopril arginine</i> , 5 -10 mg once daily <i>Perindopril erbumine</i> , 4-8 mg once daily	30–60	2.5/2 mg once daily
	15–30	2.5/2 mg alternate days
	<15	2.5/2 mg on day of dialysis
Olmesartan 20 -40 mg once daily	<30	Avoid use
Valsartan 80-320 mg once daily	<30	80 once daily
Fenofibrate 145 mg once daily	20–60	96 once daily
	10–20	48 once daily
	<10	Avoid use
Zoledronic acid ^b 5 mg once per year	<30	Avoid use
Alendronate 10 mg once daily or 70 mg once a week.	< 35	Avoid use
Ibandronic acid <i>Oral</i> 50 mg once daily <i>IV</i> 6 mg every 4 weeks	30–50	Oral: 50 every second day, IV: 4 every 4 weeks
	<30	Oral:50 once each week, IV:2 every 4 weeks
	<10	Avoid use
Risedronate 5 mg once daily or 35 mg once a week or 150 mg once a month	<30	Avoid use
Clodronate 1600-3200 mg daily	50–80	1600 daily
	30–50	1200 daily
	10–30	800 daily
	<10	Avoid use
Tiludronate 400 mg once daily	<30	Avoid use
Strontium 2000 mg once daily	<30	Avoid use
Teriparatide 20 micrograms once daily	<30	Avoid use
Duloxetine 30-120 mg once daily	<30	30 once daily
Bupropion 150-300 mg once daily	≤ 50	150 once daily
Rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily.	<15	Avoid use
Dabigatran 150 mg twice daily	30-50	110 twice daily
	<30	Avoid use
Pregabalin	30–60	300 in 1 or 2 doses

75-300 mg twice daily	15-30	150 in 1 or 2 doses.
	<15	75 as single dose.
Gabapentin 300-3600 mg daily	50-79	600-1800 daily in 3 doses
	30-49	300-900 daily in 2/3 doses.
	15-29	600 daily in 2/3 doses.
	<15	300 daily
Levetiracetam 250-1500 mg twice daily	50-79	500-1000 twice daily
	30-49	250-750 twice daily
	<30	250-500 twice daily
Memantine 5-20 mg daily.	5-29	10 once daily
Paliperidone 3-12 mg once daily	50-80	6 once daily
	30-50	3 once daily/Avoid injection
	10-30	3 once daily
	<10	Avoid use
Pramipexole 125 micrograms-1500 mg 3 times daily	20-50	2.25 once daily
	<20	1.5 once daily
Varenicline 0.5-2 mg once daily	<30	1 daily
Solifenacin 5-10 mg once daily	<30	5 once daily
Tolterodine 1-2 mg twice daily	<30	1 twice daily

^aAll recommendations are based on the Australian Medicines Handbook ^bIndication for osteoporosis

Appendix 2. Survey questionnaires

Applicability, utility, and potential barriers to the use of the available guidelines and information sources for renal drug dosing purposes: A survey of General Practitioners

We are requesting your assistance in completing this brief survey. The main purpose of this survey is to better understand general practitioners' (GPs) views on applicability, utility, and potential barriers to the use of the available guidelines and information sources for renal drug dosing purposes in the primary care settings. The overall purpose is to make recommendations on how these might be improved, if deemed desirable.

We are interested to know what information sources or guidelines you currently use for renal drug dosing purposes. We would like to know whether you perceive any barriers in accessing these guidelines or tools designed to help you with drug use in chronic kidney disease.

This survey is being distributed to GPs in Australia, and is anonymous. Aggregated information from the survey will be released but individual responses will not be identifiable or linked to your email address. There are no anticipated risks associated with this research. Completion of the survey is completely voluntary and you may withdraw at any time.

The information provided by you is strictly confidential. You or your practice will not be identified in any reports or publications that may result from this study.

Thank you for your participation!

Section A. Demographics and professional information

1. Please select your gender.	<input type="radio"/> Female <input type="radio"/> Male
2. How many years have you been practising as a GP in the community setting?	Years.....
3. Is your practice setting primarily?	<input type="radio"/> Urban <input type="radio"/> Suburban <input type="radio"/> Rural <input type="radio"/> Other.....
4. What state do you predominantly practise in?	<input type="radio"/> New South Wales <input type="radio"/> Northern Territory <input type="radio"/> Queensland <input type="radio"/> South Australia <input type="radio"/> Tasmania <input type="radio"/> Victoria <input type="radio"/> Western Australia
5. Approximately how many different patients with Chronic Kidney Disease (CKD) do you see on average in a week?	Number of patients....
6. Do you use an electronic prescribing software or electronic health record system in your practice?	<input type="radio"/> Yes <input type="radio"/> No

Go to Section 8

7. Which prescribing software system are you currently using in your practice?	<input type="radio"/> Medical Director <input type="radio"/> Best Practice <input type="radio"/> ZedMed <input type="radio"/> Genie <input type="radio"/> MedTech32 <input type="radio"/> Practix and Profile <input type="radio"/> Other....
Section B. Approach to drug dosing	
8. What is your preferred renal function measure <u>for drug dosing purposes</u>?	<input type="radio"/> Serum creatinine <input type="radio"/> Laboratory eGFR <input type="radio"/> Estimated Creatinine Clearance-calculated using kidney function estimating equation
9. For the prescription of drugs in elderly patients, do you take into account	<input type="radio"/> Estimated creatinine clearance <input type="radio"/> Serum creatinine level <input type="radio"/> Laboratory eGFR <input type="radio"/> Unsure
10. Before prescribing to elderly patients, do you evaluate the renal function	<input type="radio"/> For all new drugs for the patient <input type="radio"/> Only for certain drugs <input type="radio"/> Regularly even for a repeat prescription for chronic medications
11. How <u>practical or feasible</u> it is for you to assess renal function before prescribing a renally excreted or nephrotoxic medicine?	<input type="radio"/> Very practical or feasible <input type="radio"/> Fairly practical or feasible <input type="radio"/> Not practical or feasible <input type="radio"/> Unsure/no response
12. Do you recognise any of these as factors that restrict you from ordering a kidney function test? Please select all that apply.	<input type="radio"/> Limited time/more urgent patient issues <input type="radio"/> Cost associated for patient <input type="radio"/> Patient's non-adherence <input type="radio"/> Do not believe it is necessary <input type="radio"/> Not recommended by existing CKD guidelines <input type="radio"/> Communication barriers with the patient <input type="radio"/> Fear of being perceived as 'over-servicing' <input type="radio"/> Others.....
13. Has the availability of lab-provided eGFR changed the way you diagnose CKD?	<input type="radio"/> Yes. How..... <input type="radio"/> No. <input type="radio"/> Unsure
14. Has the availability of lab-provided eGFR changed the way you perform drug dose adjustment?	<input type="radio"/> Yes. How..... <input type="radio"/> No.

	<input type="radio"/> Unsure	
15. Do you think your referral practice to nephrologists has changed since the introduction of lab-provided eGFR?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unsure	
16. Do you use Cockcroft-Gault equation for estimating Creatinine clearance for drug dosing purposes?	<input type="radio"/> Yes. <input type="radio"/> No, I use laboratory eGFR. <input type="radio"/> Other	Go to question 16a Go to question 16b Go to Question 17
16a. While using Cockcroft-Gault equation which patient weight do you use?	<input type="radio"/> Actual body weight <input type="radio"/> Ideal body weight <input type="radio"/> Adjusted body weight <input type="radio"/> Unsure as I use the online calculators <input type="radio"/> Others.....	
16b. While using laboratory eGFR for dosing, you use	<input type="radio"/> eGFR exactly as provided by the laboratory <input type="radio"/> I take the lab eGFR provided and normalise it for the patient's body surface area for all patients <input type="radio"/> I take the lab eGFR provided and normalise it for the patient's body surface only for only patients with extremes of body weight <input type="radio"/> Unsure	
17. Please indicate how strongly you agree with each of the following statements. Bisphosphonates can be used in all stages of CKD with correct dosage adjustment. ACEi/ARBs can safely be prescribed at all stages of CKD and should not be deliberately avoided just because GFR is reduced.	<input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Neutral <input type="radio"/> Disagree <input type="radio"/> Strongly disagree	
18. Please circle the appropriate number on the 5-point scale: Not at all confident 1 to Very confident 5. How confident you are in identifying nephrotoxic drugs, renally-cleared drugs? How confident are you in determining the optimal dose for ACE inhibitors and/or ARB in patients with CKD? How confident you are on determining the optimal dose for bisphosphonates in patients with CKD? How confident you are on determining the optimal dose for glibenclamide, metformin and gliptins in patients with CKD?	<input type="radio"/> 1 – Not at all confident <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 – Very confident	

Section C. Barriers to using guidelines and how it can be overcome	
19. How often do you experience difficulties in deciding on drug dosages for patients with declined renal function?	<input type="radio"/> Often or sometimes <input type="radio"/> Rarely or never
20. Which information source do you mostly use for guidance about renal drug dosing in your practice setting? Tick only <u>one</u> option.	<input type="radio"/> British National Formulary (BNF) <input type="radio"/> MIMS <input type="radio"/> Australian Medicines Handbook (AMH) <input type="radio"/> Therapeutic Guidelines <input type="radio"/> The Renal Drug Reference Guide <input type="radio"/> Contact hospital pharmacist or consultant <input type="radio"/> Contact local pharmacist <input type="radio"/> None <input type="radio"/> Other please mention.....
21. How do you access them?	<input type="radio"/> Electronically <input type="radio"/> Paper-based
22. What is your rating of the clinical usefulness of the information source for assisting with drug dosage decisions for patients with CKD?	<input type="radio"/> Very useful <input type="radio"/> Fairly useful <input type="radio"/> Not useful <input type="radio"/> Unsure/no response
23. Can you comment on the guidelines/recommendation's reliability?	<input type="radio"/> Very reliable <input type="radio"/> Fairly reliable <input type="radio"/> Not reliable <input type="radio"/> Unsure/no response
24. Are the guidelines easy to access?	<input type="radio"/> Yes <input type="radio"/> No, it requires too much time navigating <input type="radio"/> Unsure/no response
25. Are the recommendations applicable to primary care settings?	<input type="radio"/> Very or fairly applicable <input type="radio"/> Not useful <input type="radio"/> Unsure/no response
26. Has the Kidney Health Australia- "CKD management in general practice guidelines" been helpful in managing patients with CKD?	<input type="radio"/> Yes <input type="radio"/> No, I am not familiar with them <input type="radio"/> No, I am familiar with them, but they are not useful in my practice <input type="radio"/> Unsure
27. Do you feel any of the following limit accessing the guidelines/drug information sources or performing dose adjustment in patients with CKD? Please tick all that apply.	<input type="radio"/> Lack of time <input type="radio"/> Lack of investment by health authorities for routine assessment of renal function

	<ul style="list-style-type: none"> o The information source: lack of information, ambiguous information o Lack of hard evidence o Not recommended by existing guidelines o Evidence not related to context of primary care o Too much evidence o Do not believe reduced dose will improve patient outcome o I don't know where to look for the information o Lack of easy access to guidelines o Patient factors - attitudes, expectations of patients o The need of lengthy discussions with patients o Others.....
<p>28. Data from research suggests that inappropriate prescribing of renally-cleared drugs in patients with renal impairment is not uncommon. Which of the following factors do you feel may contribute to this? Please select all that apply.</p>	<ul style="list-style-type: none"> o Insufficient information on appropriate drug doses for the particular patient o Insufficient access to dosing information during consultation o GPs not making use of information they have on drug dosing o GPs not making use of information about individual patients o Lack of routine renal function assessment o Lack of awareness on availability of information sources
<p>29. Which of the following interventions would most appeal to you to help optimise the medication for patients with CKD? Rank most important to least important as 1-6.</p>	<ul style="list-style-type: none"> o Clinical decision support systems that assist with drug dosing decisions o Academic detailing visits by a nephrologist o Pharmacist-conducted medication reviews o Online training and education o Continuing medical education lectures o Face to face and online learning modules



FACULTY OF HEALTH

School of Medicine

Dear Dr.....

You are invited to take part in a survey we are undertaking to explore general practitioners' (GPs) views on applicability, utility and potential barriers to the use of the available guidelines and information sources for renal drug dosing purposes in the primary care setting. The overall purpose of the survey is to make recommendations on how the information sources or guidelines might be improved.

You can access the survey at: <http://tinyurl.com/ogpaak8>. The survey should take less than 5 minutes to complete and you will be given an opportunity to participate in a draw for a iPad mini.

If you have any questions about your participation in the study, please contact Aarati Khanal (03 62262190). If you have any concerns of an ethical nature, or complaints about the manner in which the project is conducted, please contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (Ph.: 03 6226 6254 or email: human.ethics@utas.edu.au). You will need to quote the reference number H0015068.

Thank you for your assistance.

Yours sincerely,

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